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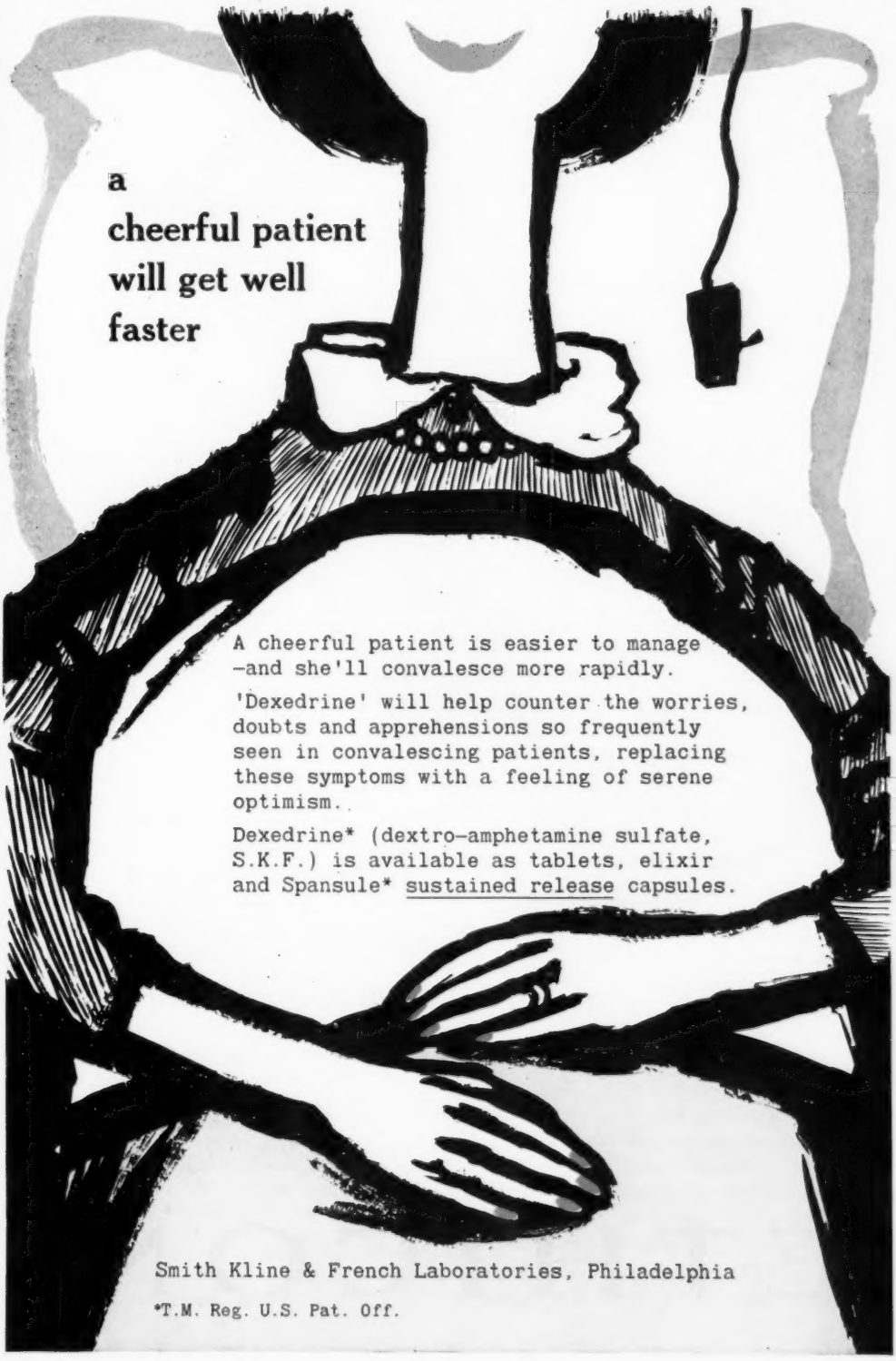
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Place of Sympathectomy in the Treatment of Occlusive Arterial Disease

GEZA de TAKATS, M.D., M.S., Chicago

Evolution of Concepts Regarding Sympathectomy

Sympathectomy for occlusive vascular disease has had a hard time. The operation having originally been proposed for spastic paralysis by Hunter and Royle, Adson,[1] in this country, and Diez,[2] in Rio de Janeiro, promptly recognized the warm dry skin following sympathetic denervation and advocated this operation for spastic vascular disorders and intractable hyperhidrosis. Since the postphlebitic syndrome often showed vasospastic phenomena, a number of clinics, notably the one at Tulane,[3] added sympathectomy for the relief of the cold, edematous extremity. The emphasis in the early years of sympathectomy was on "vasospasm," and only after Trimble's suggestion[4] was arteriosclerosis included among the indications, an idea which our group heartedly endorsed.[5]

Submitted for publication April 29, 1958.

From the Department of Surgery, University of Illinois College of Medicine, and the Presbyterian-St. Luke's Medical Center.

Presented at a Symposium on Management of Arteriosclerotic Occlusions of the Aorta and Major Arteries of the Extremities, at the Third International Congress of the International Society of Angiology, Oct. 20, 1957, Atlantic City.

The appended bibliography contains mostly the recent advances or conceptual changes in this field and a record of personal experience. Lack of space prevents the listing of many outstanding contributions, for which omission apologies are due.

After Spurling[6] reported the first cases, in 1930, causalgic pain was treated by sympathectomy with dramatic relief. Depending on the extent of the denervation and the duration of the disease, success was definite and specific if the pain was not permitted to last too long. The concept of the first, second, and third sensory neurons was evolved.[7]

Starting out as a spectacular neurosurgical procedure, it became a simple, well-standardized operation, performed by the resident staff in 30 to 45 minutes. Abuse of sympathectomy was inevitable, at least in this country. Patients with cold hands and feet, with radicular pain causing vasospasm, with low metabolic rates associated with anemia, with frank diabetic neuropathy, or with irreversible arteriosclerotic ischemia and gangrene were subjected to this operation. At times the extremity would get decidedly worse instead of better.

The reaction to such wholesale unnecessary sympathectomies came from two sources. Thoughtful physiologists and internists pointed out that vasomotor paralysis produced only a temporary increase in blood flow and that even this increase was limited to the skin, and not to muscle. Others emphasized the syndrome of paradox gangrene[8,9] following sympathectomy, which in my opinion is due mostly to preexisting arteriolar disease and which, frankly, my colleagues and I have not encountered.

More recently, with the advent of restoration of continuity by means of thromboendarterectomy and arterial grafting, some surgeons have intimated that the operation is obsolete and unnecessary. This presentation will attempt to portray our own attitude toward this problem, with emphasis on the patient who will or will not benefit from sympathectomy.

Anatomic Considerations

Much work has been done on the anatomic variations of the sympathetic chain, but for practical purposes a resection of the lumbar ganglionated trunk from the level of the aortic bifurcation to the medial crus of the diaphragm suffices for the sympathetic denervation of the lower extremity below the knee. Should one wish to influence the collateral circulation developing after an aortic, iliac, or common femoral occlusion, the inclusion of the lower two thoracic and first lumbar ganglia is imperative. This is also true if causalgic pain is to be influenced, and Mayfield has given good clinical evidence to this effect.[10] A detailed anatomic description, together with neurodissections, is found in Mitchell's monograph on the anatomy of the autonomic nervous system.[11] From this work, and the electrical stimulation experiments of Coldwater, Randall, and Hertzman,[12] it becomes obvious that the surgeon had better do a more extensive sympathectomy than has been practiced in the past because of great individual variations in sympathetic outflow. In several instances one can significantly improve the circulation of a previously sympathectomized extremity by adding a thoracolumbar sympathectomy to the customary excision of the second to the fourth lumbar sympathetic ganglia. This improvement was particularly striking in a 34-year-old man suffering from advanced thromboangiitis obliterans, who had previously lost one leg above the knee and whose remaining foot was gangrenous and intractably painful. While there has been some dissent as to the importance of high lumbar sympathectomy,[13] Leriche, Lilly, Grimson, and many others are convinced of the importance of removing the low thoracic, or at least the first lumbar ganglion, for adequate sympathetic denervation of the entire lower extremity.[14]

In the description of the physiologic effects of sympathectomy, mention will be made of the presence of afferent nerve fibers. This has been a controversial point for many years, the orthodox opinion being based on the work of Moore and Singleton[15] that no sensation of any sort from the extremities is mediated by the sympathetic chain. Yet not only is causalgic pain immediately and specifically relieved after block of the sympathetics, but the severe ischemic pain at rest in pregangrenous extremities is sometimes greatly improved, even though there is no evidence of increased blood flow. The arguments for and against afferent fibers are still unsettled. In an excellent summary on "visceral" pain, White[16] does not mention afferent sensation from the extremities, and it is sufficiently established that the threshold of cutaneous sensibility is not raised after sympathectomy.[17] Further discussion of this problem will be found under "Physiologic Considerations."

Another anatomic finding of surgical significance is the presence of sympathetic ganglia outside the ganglionated sympathetic trunk, which may thus establish connection with the periphery by bypassing the paravertebral ganglia.[18] This arrangement may well account for nondenervated cutaneous areas, manifested by residual spots and strips of sweating, especially at the 12th thoracic and 1st lumbar segments. Whether these connections are numerous enough to become foci of clinical recurrence is uncertain. Their pharmacologic suppression by ganglioplegic drugs, such as methonium, pentolinium, or chlorisondamine (Ecolid), is easily accomplished.

Physiologic Considerations

Sympathectomy interrupts efferent vasoconstrictor and vasodilator fibers to the ex-

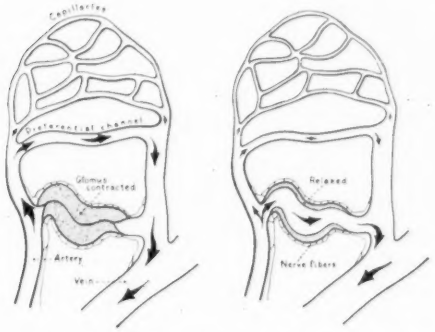


Fig. 1.—Normal glomus in a contracted and relaxed state. When the shunt is closed, the blood passes through the arteriolar-capillary bed, including preferential channels. When the shunt is open, the terminal vascular bed receives only a part of the arterial blood. The venous blood shows high oxygen saturation. Such a condition exists shortly after sympathectomy, during the vasodilator phase of cold injury, and also after epinephrine, arterenol, posterior pituitary injection U. S. P. (Pituitrin), and fainting, as a result of capillary constriction. From article entitled Fundamental Factors Affecting Vascular Surgery, by G. de Takats, published in *Surgery* (41:444, 1957), reproduced by permission of The C. V. Mosby Company, St. Louis.

tremities. Some of the clinical observations following sympathectomy have recently been summarized.[19] During the immediate period of vasodilation after sympathectomy the arteriovenous shunts are open (Fig. 1) and venous oxygen saturation rises appreciably

Effect of Sympathectomy on Venous Oxygen Saturation

	Patient	Oxygen Saturation, % *
1	Operated side	82.0
	Control side	30.6
2	Preoperative	62.9
	Postoperative, 12th day	77.4
	Postoperative, 56th day	79.0
	Unoperated side	44.0
3	Preoperative	77.4
	Postoperative	85.7
4	Operated side	76.2
	Unoperated Side	58.4
5	Operated Side	73.6
	Unoperated Side	42.5

* Average rise in O_2 saturation, 34% (Hick, F. A., and de Takats, G., 1936, unpublished experiments).

(Table). If the opening of the shunts, however, is not followed by a compensatory increase in blood flow because of widespread occlusive arterial disease, the digits become pale, cooler than before, and a *paradox drop* in skin temperature develops during a sympathetic block. In such a case (Fig. 2) sympathectomy may have to be combined with minor amputations, a situation which frequently arises in cases of thromboangiitis obliterans.

The shunts, bypasses, alternate pathways, and muscular sphincters (Fig. 3) are regu-

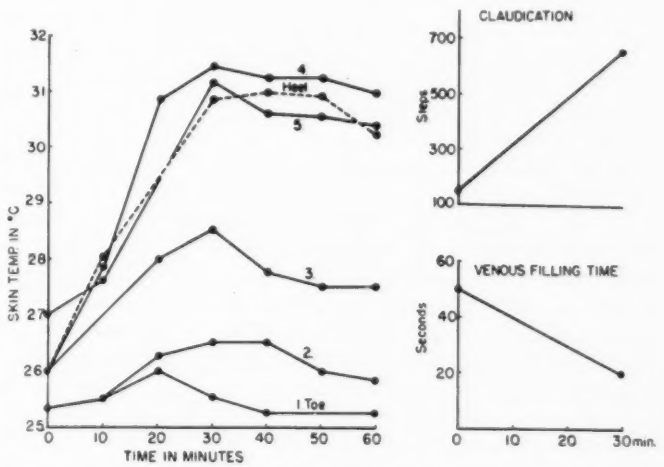


Fig. 2.—Effect of sympathetic block on skin temperature, claudication, and venous filling time. The temperature of the heel and fourth and fifth toes rises to the level of normal vasodilation. The skin temperature of the third toe shows a moderate rise, but the temperature of the first and second toe shows no appreciable rise. Claudication distance increased from 150 to 650 steps; venous filling time decreased from 50 to 20 seconds. Lumbar sympathectomy *with simultaneous amputation of the first two toes* resulted in an excellent anatomic and functional recovery. From article entitled Value of Sympathectomy in Treatment of Buerger's Disease, by G. de Takats, published in *Surgery, Gynecology & Obstetrics* (79:359, 1944), by permission of the Surgery Publishing Company, Chicago.

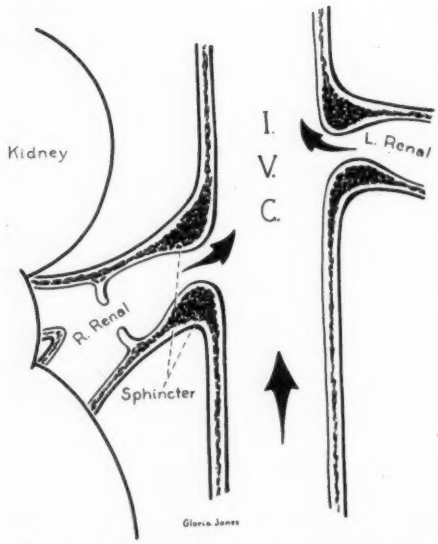


Fig. 3.—Muscular sphincters at the entrance of the right and left renal veins into the vena cava. Their function in the human adult is unproved, and they atrophy with growth and aging. They are likely to be under dual, i. e., hormonal and neurogenic control. (Redrawn from illustration in "A Primer of Venous Pressure," by G. E. Burch, 1950, and reproduced by the courtesy of the author and by permission of the publishers, Lea & Febiger, Philadelphia.

lated by the sympathetic nervous system, but are also under hormonal control. Thus, epinephrine, arterenol, and posterior pituitary injection U. S. P. (Pituitrin), which are activated during stress, may maintain open shunts by closing capillaries, resulting in a rise of venous oxygen saturation.[19]

There has been some uncertainty as to whether or not such arteriovenous shunts exist in skeletal muscle. Recently, however, the microinjection studies of Saunders[20] have conclusively shown their existence. Thus, the hypothesis of Barcroft and his co-workers[21] has received anatomic confirmation. Barcroft believes that a dual circulation exists in muscle: (1) anastomotic, consisting of arteriovenous shunts, bypasses, and preferential channels, which are regulated by the vasomotor center, and (2) nutritive, consisting mostly of the capillary bed, which is controlled by metabolites and functions without nervous control.[22]

The existence of this dual circulation explains why radioactive-sodium-clearance techniques do not reveal any increase in the circulation of muscle (i. e., calf or forearm) after reflex heating or sympathetic block. Obviously, the sodium clearance does not pick up an increased blood flow through the anastomotic channels. Yet plethysmographic studies do show an increased blood flow after release of vasoconstrictor tone, and certain carefully selected patients do exhibit an improvement in claudication after sympathectomy.[5]

It is necessary to emphasize the effect of sympathectomy on muscle-blood flow, since many observers, notably Abramson, have long emphasized that improvement in circulation is limited only to the skin,[23] and does not include muscle.

The changes in blood flow following sympathectomy can be best studied on limbs sympathectomized for hyperhidrosis or deep venous thrombosis, where the arterial tree is intact. Such a record is shown in Figure 4, through the courtesy of Walker, Lynn, and Barcroft.[24] There is an abrupt rise in blood flow within a day or two after sympathectomy, the flow decreasing within two weeks to about twice the preoperative level. There is on the average an eightfold increase in the hands and about a fourfold increase in the feet. At the same time, the finger and toe temperatures rise but do not fall concomitantly with the decrease in blood flow. In well over 1000 lumbar sympathectomies performed on my service for occlusive arterial disease, the toe temperatures on the sympathectomized side often remained 6-8 degrees (F) higher than the ones on the nonsympathectomized side. Some of the observations relate to patients operated upon more than 25 years ago.

The early return of blood flow to slightly above the preoperative level is commonly explained by the regain of intrinsic tone.[22] The final increase in the rate to twice the initial level may make just the difference between survival of the limb and gangrene. Furthermore, in occlusive arterial disease

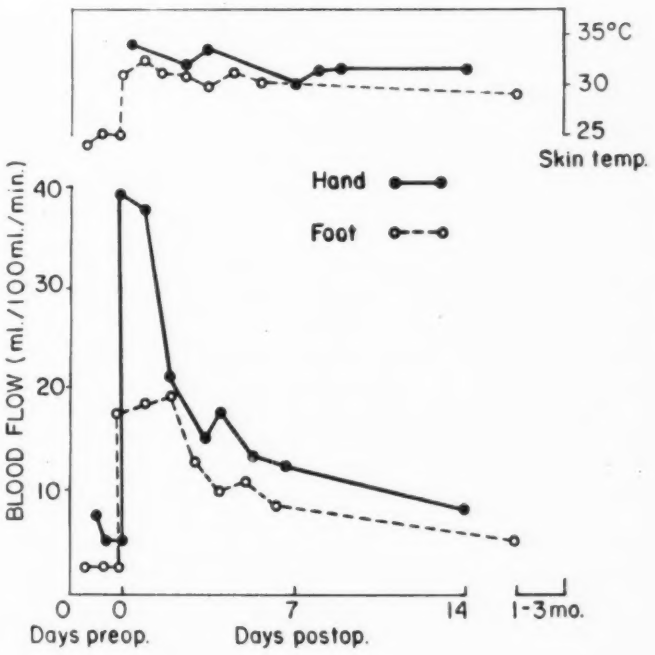


Fig. 4. — Changes in blood flow following sympathectomy compared with the rise in skin temperatures. Straight lines refer to the hands; interrupted lines, to the feet. Skin temperatures are on top; blood flows are below. Note the abrupt rise in blood flow within a day or two following operation, which decreases to about twice the preoperative level in 14 days. Skin temperatures, however, remain elevated. Redrawn from article entitled On the Circulatory Changes in the Hand and Foot After Sympathectomy, by A. J. Walker, R. B. Lynn, and H. Barcroft, published in *St. Thomas' Hospital Reports* (6:18, 1950), reproduced by permission of St. Thomas' Hospital, London.

one does not encounter the early spectacular rise in flow, so that the difference after the regain of vascular tone is not as great.

While the permanent basal blood flow after sympathectomy in the resting state is only about twice the preoperative level, vasoconstrictor paralysis frees the extremity from the influence of erect posture, reflex cold, and emotional stimuli. Thus, as has frequently been expressed before, it is as though the sympathectomized limb were horizontal in bed, wrapped in cotton, in the southernmost strip of Florida, and freed of hypothalamic impulses, as if its owner were in a state of euphoria or under the effect of tranquilizers.

The elimination of sympathetic vasodilator impulses, which definitely exist in man,[25] does not seem to decrease postcontraction hyperemia of the exercising muscle.[26,27] The sympathectomized extremity cannot be warmed, even if it has adequate arterial pathways, by heating another part of the body, because the response is mediated by sympathetic vasodilators. Other forms of vasodilation acting directly on neuromuscular junctions or on posterior root cholinergic vasodilators are now unopposed by vasomotor tone and thus become more active.

Thus carbon dioxide inhalation produces a vasoconstriction in the normal limb, but in some of our sympathectomized patients Gellhorn and Steck[28] found an increase in blood flow, since the peripheral vasodilating action of this gas could act unopposed. Both cholinergic and adrenergic stimulation, effected, for instance, by neostigmine and nylidrin (Arlidin), respectively, was active after sympathectomy. As will be pointed out in the clinical part of this paper, nylidrin seems especially beneficial in the sympathectomized extremity, and if the operation has been done in the presence of marked intermittent claudication, this drug is part of our postoperative management.

On sympathetic stimulation, adrenergic and cholinergic substances are liberated, but they are promptly inhibited by locally acting enzyme systems. Epinephrine and arterenol are secreted on efferent sympathetic

stimulation, but they rapidly disappear on being exposed to amine oxidase. This enzyme is unusually sensitive to slight reductions in oxygen tension.[29] Since sympathectomy demonstrably increases tissue oxygen tension, it is likely that it helps to eliminate these locally acting vasoconstrictors, which may even produce Raynaud's phenomena in ischemic digits.[19]

It is customary to explain the increased blood flow after muscular contraction by the production of vasodilator substances. Certainly, as pointed out before, sympathectomy does not influence the postcontraction hyperemia. Nevertheless, there is now evidence that axon reflexes are involved in the increased blood flow to exercising muscle, since local infiltration of procaine can abolish the hyperemia.[27] This must be then, just as in a cutaneous histamine flare, the result of efferent cholinergic vasodilation and should be absent in a limb whose sensory nerves have degenerated. In an arteriosclerotic extremity exercise will decrease oscillations, instead of increasing them. Such a record indicates either a collateral type of blood flow or a terminal destruction of the muscular arterial bed. The latter is obviously difficult to influence by any method but still shows postcontraction hyperemia.

A final significant observation of Cooper and Kerslake,[30] which we have recently confirmed, should be mentioned. It relates to the presence of afferent fibers in the sympathetic nervous system of the extremity. There is no actual conduction of painful sensations; there is no elevation of cutaneous sensory threshold, but the rise in skin temperature which one obtains after immersion of a limb in hot water will fail to appear in another extremity when the immersed limb is sympathectomized (Fig. 6). In other words, the direct reflex component of the Gibbon-Landis test is abolished, while the delayed indirect response, due to the warming of the heat center, is not interrupted.

This simple clinical experiment, which can be readily reproduced with cold as well as heat, may have wide clinical application. Can it explain the abolition of causalgic pain after sympathectomy, and can it explain the disappearance of deep, boring "visceral pain" in the postphlebitic syndrome? A cake of ice can be held much longer in the sympathectomized hand than in the nonsympathectomized hand. Is this due simply to the higher initial skin temperature of the sympathectomized side? Is the sympathectomized skin, often 10-15 degrees (F) warmer than the control extremity, simply unable to register—through somatic fibers—the slight temperature difference between itself and the warm bath, whereas the nonsympathectomized extremity is exposed to a differential of 10-15 degrees (F)? Such and many other questions will have to be investigated in the future.

Indications for Sympathectomy

Obviously, the indications for an operation like sympathectomy, which does not remove a diseased organ or tissue, are closely controlled by the results obtained in various forms of occlusive arterial disease. Since only organic arterial disease is included in this discussion, many other neuromuscular disturbances, such as Raynaud's phenomena, causalgic states, cold injuries, the postphlebitic syndrome with vasospasm, the vasospastic poliomyelitic limb, and various forms of visceral pain[31] will not be discussed, nor will the treatment of hyperhidrosis by sympathectomy be considered.[32] The surgical treatment of hypertension, on which my associates have recently reported on the basis of 10- to 22-year follow-up studies,[33] is also outside the scope of this presentation.

Thus, essentially three vascular syndromes are left for discussion, i. e., *acute arterial occlusion, thromboangiitis obliterans,* together with obscure forms of *digital thrombosis,* and *peripheral arteriosclerosis.* In all three forms of organic arterial disease, the timing and the extent of operation are important factors in obtaining one's objectives.

A. Acute Arterial Occlusion.—Dramatic closure of a major artery by an *embolus* originating from the heart or an atheromatous plaque, or a mural thrombus of an aneurysm, of course, calls for immediate removal. There are, however, a number of patients who do not present themselves during the optimal 6 to 12 hours following arterial embolism. They may not be diagnosed as such; they may refuse hospitalization, or the embolus is almost silent when the patient is bedridden, hypotensive, after a coronary occlusion or in congestive heart failure. Only after a week or two does it become obvious to the patient and the attending physician that a major arterial occlusion has taken place.

The important contribution of Olwin and his co-workers [34] on the effect of late embolectomy has shown that even after a week or two an embolectomy may successfully restore arterial continuity. We have actually reamed out such arteries, doing a thromboendarterectomy, the femoral segment being a far more favorable location then the femoropopliteal one. Intense preoperative and operative heparinization, with avoidance of postoperative administration, has been useful. But all these patients—since the date of the occluded segment is uncertain—are subjected to a sympathectomy, either at the same time or as a preliminary step. Young to middle-aged women with rheumatic mitral stenosis and auricular fibrillation have had sympathectomy, extraction of the embolus, and, later, mitral commissurotomy for complete rehabilitation. Since this combination of sympathectomy with an attempt at restoration of arterial continuity will be discussed again and again, its rationale will be summarized under "Comment."

An arterial *thrombosis* originating at the level of a stenosing atheroma or during a sudden closure of an aneurysmal sac is, however, a more difficult surgical problem. Here, too, as soon as possible, and if the patient's general cardiovascular status permits, a sympathectomy and thromboendarterectomy should be done. The results of the latter, if done at the popliteal segment, are very doubtful, since the success of reopening the artery will depend on the state of the distal, subpopliteal segment. Owing to the lack of *adequate back-flow* from below, the thrombectomy is bound to fail, and the fate of the limb will depend on the amount of help sympathectomy can offer. The point to be made here is that it is advisable to do the preliminary sympathectomy *first*, and not wait for the thrombectomy to fail, or to do it when the exploration of the distal segment proves that a "direct" attack on the occlusion is impossible. A sympathectomy after such a situation is like opening an umbrella after being rained on.

B. Thromboangiitis Obliterans. — Here, again, the timing of sympathectomy and proper preoperative study are most important. In the presence of an active process, when there is acute periphlebitis, infected ulceration, or spreading gangrene, sympathectomy should not be undertaken. Sodium thiosulfate given daily in 1 gm. (15 grain) doses, together with intensive antibiotic therapy in case of toe infection, will cool off the active process and permit sympathectomy. In the acute phase, the clotting mechanism is so active that simple diagnostic venipunctures may result in thrombosis. The patient is resistant to heparin [35] and needs preoperative sulfur compounds or heparin.[36] Operation in this phase may produce extensive venous and arterial thromboses or pulmonary embolism.

Another limiting factor of success is the extent of terminal vascular damage. Digital arteries extending to the posterior tibial and radial arteries are frequently involved and the red, shiny, atrophic, ulcerated digits are well known. As shown in Figure 2, such digits may not warm up after sympathetic block, and the question of simultaneous amputation at the time of sympathectomy frequently arises. Again and again, one is willing to accede to the wishes of the patient that the toes are fingers be spared until the effect of sympathectomy becomes

apparent. In my case records, I find a number of cases of severely ulcerated, gangrenous toes which were amputated at the metatarsal level at the time of sympathectomy, and there is no doubt about the property of such a procedure. There is, however, a group of doubtful toes—ulcerated, cold, red, shiny—which should be removed according to past experience but which are allowed to remain, only to result in much disability, much suffering, and, finally, amputation, with delayed healing possible at a higher level.

René Fontaine, making rounds with Allen Kanavel and me at the old Wesley Hospital in 1923, first made me aware of utilizing initial hyperemia following periarterial sympathectomy to obtain rapid healing in minor amputations. While we have practically abandoned periarterial sympathectomy except in the iliac segment, to include Mitchell's "iliac nerve," [20] our service has always felt that postsympathectomy amputations at critically low levels have less chance of succeeding unless they are within the limits of the massive hyperemia of the first two weeks (Fig. 4). The amputation of one toe, or a high metatarsal amputation, gives surprisingly steady, nonvulnerable feet, and the loss of the first metatarsal head, contrary to orthodox orthopedic opinion, does not inconvenience the patient.

When thromboangiitis obliterans affects and closes the femoropopliteal or the iliofemoral segment, such as in my experience occurs only in neglected or ill-treated cases, the sympathectomy has to be high, including the first lumbar, and possibly the last two thoracic, ganglia. One does see patients with supracondylar amputations for Buerger's disease, but so far we have never had to do one provided that sympathectomy and lower-leg amputation are combined.

In a group of digital thromboses [37] occurring in middle-aged, heavy-smoking men, who use their hands excessively, such as chiropractors, automobile mechanics, pianists, or stenographers, thoracic sympathectomies, removing the second to the fifth ganglia with an axillary transthoracic approach, have been exceptionally useful in healing ulceration, relieving pain, and allowing full use of the hand. Whether these digital thromboses are atypical forms of Buerger's disease, affecting no other part of the vascular system, is uncertain. The endarteritis proliferans of frostbite and of air-hammer disease belongs to this same category. In this group, however, the vasospastic element and the hyperhidrosis are accompanied by neuropathy of various degrees, which is uninfluenced by sympathectomy. In fact, the severe burning pain of neuropathy may be aggravated and is regarded as a contraindication to sympathectomy in cold injuries.

One final word about hyperhidrosis, which frequently accompanies thromboangiitis obliterans in its early stages and stops only when the circulatory embarrassment is advanced: drying up the feet and hands of patients suffering from Buerger's disease immediately eliminates fungal infection and stops the bromhidrosis of hyperhidrosis.[32]

C. Peripheral Arteriosclerosis. — While patients suffering from arteriosclerosis obliterans carry various degrees of vasomotor tone, arteriosclerotic limbs do not usually exhibit any unusual amount of vasospasm. Release of vasomotor tone, however, seems to affect favorably arteriosclerotic circulation, as pointed out under the heading of "Physiologic Considerations." The percentage of improvement may be as low as 31% to 35% [38] or as high as 87%,[40] and this wide variation is obviously due to one of two factors, i. e., case selection and progressive course of the disease. Since we are here concerned with indications, the first factor should be briefly discussed.

Peripheral arteriosclerosis is better understood today than at the time sympathectomies were first done for it.[4,5] Arteriography has been of great help. We know that there are stenosing atheromas at the aortic, femoral, and popliteal bifurcations, in the iliac segments, and at Hunter's canal which lead to claudication, but only after

six to eight blocks, and which manifest themselves by pulsations of fair strength, but diminishing after exercise.[41] In such a situation sympathectomy followed by thromboendarterectomy is the method of choice. The latter operation, however, shows many late failures, and I have personally limited its use to the aortic-iliac segment, *always preceded by sympathectomy*, because the fate of the reamed-out vessel is never certain and because a sudden closure at a later date might find the collateral circulation utterly unprepared.[42]

Another type is that of short segmental obliteration with functioning collateral circulation, and these patients do very well with sympathectomy. The question immediately arises about a segmental resection or bypass, and much depends on the site of occlusion. The short occlusion of the aortic bifurcation, the typical Leriche syndrome, does outstandingly well with an end-to-side anastomosis, provided the distal arterial tree is fairly free (it is never quite free) of disease. Second obstructions at Hunter's canal should be attacked at the same time. Popliteal occlusions have not done well with attempted restoration of continuity in personally observed cases, and the lower the occlusion the more definitely the sympathectomy is indicated. This, of course, is not true of the terminal micromesh of the muscles or of the cutaneous arterioles, the destruction of which is not within surgical means. According to Luke,[43] claudication in the popliteal arterial occlusion is definitely improved immediately after sympathectomy. This has not been our experience, but the operation is done as a limb-saving procedure.[44] All vascular reconstructions should be preceded by an adequate sympathectomy, for the reasons advanced in the previous paragraph. Since sympathectomy decreases collateral resistance, it will facilitate the run-off in the distal segment; and should thrombosis occur, the limb has a better chance of surviving.

In diffuse, obliterating, or stenosing arteriosclerosis, where the vessels are ulcerated, calcified, stenosed, or thrombosed from the diaphragm to the pedal vessels, the benefit derived from sympathectomy will depend on the extent of collateral circulation or, shall one say, the capacity of the terminal vascular bed to dilate. Failure to observe this rule will lead to ulceration or gangrene. Since this point is such an important one, simple measures for the estimation of available collateral circulation should be carried out.

At our institution, procaine block of the posterior tibial nerve or at the level of the lumbar sympathetic ganglia is not done in all patients but is carried out in those in whom terminal circulation is in doubt. This doubt arises when a thin wrap of absorbent cotton from toes to knee does not warm up the toes to room temperature. Since many institutions today have air-conditioned operating rooms and anesthesia rooms, this controlled temperature is sufficient for temperature studies. A McKesson Dermalor is used for measuring skin temperature.

In these studies we are interested not so much in a rise as in the absence of rise or fall in skin temperature. On a large vascular service one would not advocate, except for teaching purposes, a routine use of these diagnostic blocks. For the doubtful case, it gives a good idea of impending circulatory failure of terminal circulation.

Briefly, then, sympathectomy is indicated in stenoses and in segmental and diffuse arteriosclerosis, and, should "direct surgery"[45] be contemplated, the need for sympathectomy is even more definite.

Results

Several years ago, the *Journal of Clinical Investigation* announced an editorial policy. No paper was to be accepted for publication unless the data were presented and analyzed as to their statistical significance. On the basis of this criterion, I should be unable to present my experience. While one can readily analyze 100 arterial grafts and the state and number of closures, hemorrhages, and patencies after a period of

two years or less, the variables in evaluating sympathectomy for occlusive arterial disease are so many that a meaningful group of data will not emerge, in my opinion.

In the first place, the objectives of this operation vary from relieving claudication to healing of ulcerations and spontaneous demarcation of gangrene. Saving a leg from amputation and relieving rest pain is an optimal result in one case, but increasing walking ability from one to three blocks is the desirable objective in the other. Classifying peripheral arteriosclerosis into four grades, as we have done in our clinic since 1939,[46] helps to form our objectives as to how much can be expected and accomplished by sympathectomy.

Second, the operation neither removes nor influences the vascular disease for which it is undertaken. If thromboangiitis continues to spread, regress, and recur, if arteriosclerosis continues to close more vessels by atheroma and thrombosis, the 5- or 10-year results of sympathectomy will be obviously vitiated. Yet the sympathectomy did perform the service it was expected to, for the circulatory status prevailing at the time of the operation.

This brings us to the third difficulty in evaluating results, especially of a collective nature, where the management of cases varies from one institution to another. Suppose all patients suffering from peripheral arteriosclerosis are placed postoperatively on a low-fat diet, as started by Nelson Barker in 1936 [47] and followed rigorously by us ever since, has one introduced here a significant factor? Or suppose the patient has had an arterial bypass or an endarterectomy with the sympathectomy, has this combination been superior? One may speak of impressions, of dramatic improvement, but nothing of statistical significance.

There have, of course, been a number of reports giving the percentage of failures, improvements, and lack of improvements, and the monogram of White, Smithwick, and Simeone [16] has summarized them up to 1953. Our own figures have been included in their tabulations, and yet the variability of material is so great that a true picture of the help that sympathectomy offers in the total management of organic vascular disease is not clear-cut or clearly defined. In the literature, improvements have been reported in as high as 93% and in as low as 50% of the cases.[13] For this reason, I have put down the types of cases in which sympathectomy will predictably do the job which the patient can expect from it and also try to outline situations in which sympathectomy is useless or harmful. In other words, exact indications should ensure a minimum of failures.

In the *postembolic and post-thrombotic occlusions*, sympathectomy salvages all viable tissue. It may hasten gangrene, but only in that it hastens demarcation and permits an earlier and more definite level of amputation. In the less severe occlusions, meaning that thrombosis distal to the occlusion has not obliterated collaterals, sympathectomy decreases the vulnerability of the skin to future damage and, if sufficiently high, improves ischemic neuritis. Should the acute occlusion be relieved by embolectomy or thrombectomy, sympathectomy need not be done unless residual distal thrombosis is marked.

In *thromboangiitis obliterans*, because of the protean and unpredictable nature of the disease, sympathectomy is always indicated, but, as pointed out before, not in the acute stage. Gangrenous or pregangrenous digits which do not warm up on diagnostic block are simultaneously amputated. A flare-up of the disease in the sympathectomized extremity is not uncommon, but this has to do with trauma, tobacco, exposure to cold, or poor foot hygiene. In a "burned-out" case of Buerger's disease sympathectomy shows lasting results.[36]

The same is true of digital thrombosis and the vascular and vasomotor sequelae of cold injuries. In an acute frostbite demarcation of gangrenous toes and digits will be rapid, and the edema above the gangrenous areas will subside. Convalescence and

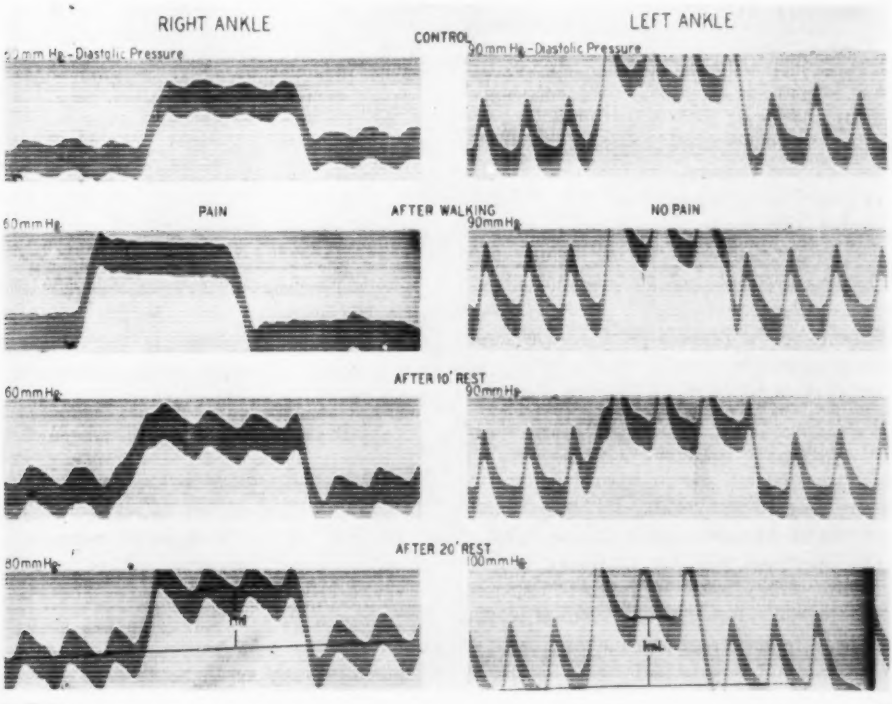
discharge from the hospital is roughly cut down six to eight weeks, and the skin of the stump is less vulnerable. In neuropathy due to chilling, however, the burning dysesthetic foot or hand will not improve. In the follow-up studies of veterans of World War II this burning pain may have been aggravated, but it is likely that the psychogenic element here is of considerable significance.

In arteriosclerosis obliterans, graded according to severity into four groups, the following results have been obtained:

In Grade I, with the patient's claudication appearing only after two to six blocks, a warm foot, well-maintained but diminished pulses or good pulses, oscillations decreasing on exercise, and the arteriogram showing stenosis or short occlusion, with short, sturdy collaterals, sympathectomy will markedly increase walking ability, but this improvement may take six months to a year for its full development. This development of collateral circulation following sympathectomy is definitely increased by the administration of nylidrin hydrochloride (1 to 2 tablets [6 mg. each] three times a day) and systematic walking to the point of tolerance, a method which seems to be excellent in producing postcontraction hyperemia (Fig. 5).

Thromboendarterectomy and arterial grafting are discussed by other authors in this symposium. There is no doubt about their striking value at aortic and iliofemoral segments, and we have used them selectively in segmental femoral occlusion. Since multiple occlusions may exist, especially below the groin, I have always insisted on a preliminary sympathectomy, a procedure

Fig. 5.—Oscillometric tracings recorded with Carl A. Johnson's apparatus before and after walking. Note the minimal pulse waves at the right ankle, which disappear at the time of pain on exercise. After 10 and 20 minutes of rest there is considerable increase of the waves. On the left, unaffected side, the peaks are sharp and high at rest; they become higher on exercise and maintain the same spikes after 10 and 20 minutes. The pulse waves on the affected side show a lengthened crest time and blunted peaks.



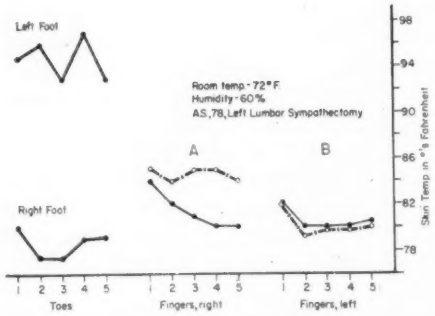


Fig. 6.—In the case of a 78-year-old man with arteriosclerosis, a left lumbar sympathectomy was done eight months previously. On the left of the graph the toe temperatures of the two feet are shown, with a sizable difference between the sympathectomized and the nonsympathectomized side. At *A*, the right, nonsympathectomized lower leg and foot were immersed in hot water; the fingers of the right hand showed a rise in skin temperature within one to two minutes. At *B*, the left, sympathectomized lower extremity was immersed in equally hot water (100 F). No rise in temperature of the fingers of the left hand developed. The preimmersion temperatures of the two hands showed very little difference, and there was no detectable vascular disease in them. The determinations were made in an air-conditioned room with 72 F temperature and 60% humidity. The lack of thermal response of a sympathectomized limb to a cold stimulus in a hot room is equally demonstrable. Unpublished data.

not followed by some leading exponents in the field.

In Grade II, that of peripheral arteriosclerosis, claudication begins after less than two blocks; the feet are cold and pulseless in a cool environment, but there is demonstrable vasomotor activity with sweating. The arteriogram shows more extensive occlusion, possibly multiple segmental occlusions. Circulation depends on the profunda femoris or the peroneal artery. There may be some cardiovascular-renal disease, and acute thrombosis in the coronary arteries or at the periphery is frequent. There is no trophic disturbance.

Such patients should have a sympathectomy to give them some, but not absolute, protection against sudden initial ischemia. The operation will not markedly improve walking ability, and this should be explained beforehand. Here the two restorative procedures, endarterectomy and bypass, are much more definitely indicated. The limitation of these procedures will be discussed by other members of this symposium. But, again, it should be emphasized that the nonobservance of the principle of preliminary sympathectomy may lead to loss of limb or marked aggravation of symptoms.

In Grade III, the patient can hardly get around and is unable to perform any work. He has high and low arterial occlusions, with insufficient collaterals. The foot and toes are cold. The venous filling time may be as long as 120 to 180 seconds. Briefly, the foot is in a pregangrenous state, with more or less rest pain, depending on the patient's emotional make-up or the presence of diabetes. In such a situation the results of sympathectomy are doubtful. It will not restore the patient's walking ability, but may help his rest pain. Whether or not a year or more after sympathectomy a sudden popliteal thrombosis will produce gangrene cannot be foretold. Most of the failures of sympathectomy reported from large vascular clinics come from this group. Only a careful individual study can determine whether or not the sum total of major arterial and terminal occlusion, including the destruction of arteriovenous shunts and of the micromesh in the muscles, is so extensive that sympathectomy cannot succeed. Working in vascular clinics for a year or two may be of more practical guidance than any set of expensive diagnostic criteria in accepting or rejecting such patients. The slogan "it can't do any harm" is of no help and may explain some of the high percentages of failure reported in the literature.

To Grade IV belong patients with intractable rest pain, massive gangrene, cadaveric pallor, or deep cyanosis, mostly an irreversible process, for which amputation should not be delayed too long. Here, again, the policy of "let us try sympathectomy first" is to be deplored unless it is done to lower the level of amputation. Therefore, we do not advocate sympathectomy for a patient who obviously needs a supracondylar amputation; but should a below-knee amputation be under considera-

tion, an operation is logical. One can also convert possible lower-leg amputation into a high metatarsal one with the same procedure.

I am aware that this argument requires statistical confirmation. Warren is unsure that such benefit is demonstrable.[48] Here, again, unless the two operations are done simultaneously, the benefit of the early increase in blood flow to the stump is lost, and the postcontraction hyperemia in the amputee is not so readily obtained.

There are a few other situations in which sympathectomy is of doubtful or no value. In diabetes, the arteriosclerotic lesion may be influenced to the degree that the nondiabetic sclerotic limb is improved. The terminal lesions, however, are more frequent, and neuropathy plays an important role in the success or failure of sympathectomy. Diabetic neuropathy in our experience[49] consists of an earlier, irritative phase, with much pain, some hyperhidrosis, and even vasospasm. Later a painless, anesthetic state supervenes, with vasomotor paralysis. Such a foot is warm and dry and is sympathectomized. Sympathectomy is useless and unnecessary. Then there is a syndrome of cord and posterior root involvement leading to pseudotabes. Only the first type of neuropathy is suitable for sympathectomy, and even here the vascular status determines the indication, because the neuropathy is more influenced by massive doses of cyanocobalamin U. S. P. (vitamin B_{12}) than by increasing the circulation to the vasa nervorum. Since diabetic neuropathy may occur without the slightest evidence of vascular involvement, this *metabolic neuropathy* will not be influenced, whereas the ischemic neuropathy may be. This uncertainty explains the fact that diabetic neuropathy per se is not a clear-cut indication for sympathectomy, contrary to an encouraging report,[50] and, while the patient may be pleased that the toes are warm and dry, the numbness and pain usually persist. Sympathectomy is of no use in the hot, burning, osteoporotic foot in the terminal stage of arteriosclerosis. Such a state does exist in erythromelalgia, where sympathectomy may give a brilliant result.[16,51] But in true erythromelalgia, a very rare phenomenon, all pulses are open and bounding, and vasoconstriction with dextrol amphetamine (Dexedrine) and antihistaminics has been of great help. In this arteriosclerotic terminal hyperemia, the capillaries seem paralyzed, the arteriovenous shunts are rigidly patent, and there is no adequate inflow of blood from major arteries. With or without a sympathectomy, such a leg will have to be amputated.

Causes of Failure

From the foregoing it is obvious that sympathectomy will fail to improve claudication, abolish rest pain, and save the limb from amputation (1) when there is no capacity for the vascular bed to dilate, (2) when there is insufficient collateral circulation because the extent of main-trunk obstruction is too great, and (3) when the lesion is not circulatory in origin and an increase in circulation cannot effect improvement.

Sympathectomy for the postphlebitic syndrome is generally contraindicated. In fact, as aptly pointed out by Linton,[52] a sympathectomy disease is produced, with increase in pain and increase in venous pressure because of venous congestion. In our work, only the patients with minimal swelling and superficial varicosities, but with typical causalgia-type of pain and hyperhidrosis, have been subjected to sympathectomy. This is an infrequent syndrome, occurring in from 5% to 10% of postphlebitic limbs.

Mortality and Morbidity

Lumbar and thoracic sympathectomies done by extraperitoneal and transthoracic routes, respectively, have minimal mortality. In my personal experience, the first patient subjected to a transabdominal sympathectomy, in 1928, developed evisceration and a coronary occlusion and died. He was operated on for thromboangiitis obliterans but

had diffuse arteriosclerosis with old myocardial infarcts.

No further deaths have been found in our material in the last 1000 cases related to sympathectomies performed since 1928. Some of the side-effects related to the removal of the lumbar and upper thoracic sympathetic chains were reported by Fowler and myself [53] in 1949. Infection has not been a problem independent of its prevailing incidence in the operating room. Jesser and I [54] reported on this prior to the advent of antibiotics and sulfonamides. Sympathectomy is always avoided in the presence of a spreading infection or an infectious skin lesion. Drainage of infected hematomas occurs, and in one case a severe empyema, necessitating open thoracotomy, was encountered. All transthoracic operations are now drained under water-seal for 48 hours, but for many years an anterior transcervical and, later, a posterior approach, both extrapleural, were used. In a posterior retropleural approach combined with rhizotomy, severe spinal-drainage headache with a retropleural accumulation of spinal fluid was encountered. This fluid sealed itself off and was absorbed spontaneously. I have not in recent years resected the intraspinal roots, as originally described by Smithwick,[55] although for many years we followed this excellent procedure.

Hematoma from injured intercostal or lumbar veins may present a problem. Since full exposure and full illumination with a head lamp are employed, and since a dry field is insisted on, with a restored blood pressure—should it have dropped—there has been no trouble on this score. I know of a few cases of severe hemorrhagic shock occurring after sympathectomy, but they have, fortunately, not occurred in this material. In diabetic and hypertensive patients we have paid special attention to capillary fragility, administering 300 mg. of ascorbic acid and 300 mg. of hesperidin daily, since the observation made on hypertensive patients that the pleural fluid was markedly hemorrhagic after splanchnicectomy, when capillary fragility was increased.

Cerebrovascular insufficiency or thrombosis has been recognized five times. A previous stroke is a contraindication not to sympathectomy but to spinal anesthesia. Maintenance of an even blood pressure during operation is obviously important. This complication, unless due to an embolus from a cardiac source, is mostly the result of anesthetic management, but the inclusion of severe cardiovascular cripples undoubtedly increases this complication.

Coronary insufficiency and thrombosis do occur after any form of surgery in patients afflicted with vascular disease. Over one-half of our sympathectomized patients exhibit abnormal electrocardiograms, but the following rules are observed in selecting patients for operation: 1. At least four months should have elapsed since an acute myocardial infarction. 2. In congestive failure, patients must be adequately digitalized and compensation established before the operation is undertaken. 3. Both in congestive failure and in auricular fibrillation patients are given heparin preoperatively, 100 mg. daily for three days, to saturate their mast cells.[56]

Interestingly enough, such patients stand sympathectomy—a comparatively minor and atraumatic procedure—very well. Only if a second trauma supervenes may coronary thrombosis develop. Thus, in a 55-year-old diabetic with an abnormal myocardial pattern, a prostatic obstruction occurred postoperatively. After cystoscopy he experienced a chill, and immediately after this a coronary thrombosis developed, from which he recovered. Another diabetic, aged 49, with no cardiac symptoms but with a cardiogram indicating partial heart block, tolerated a lumbar sympathectomy well and left the hospital on the 10th day. At home, after paring a callus, he developed a rapidly spreading infection and required a lower-leg amputation. A few days after this second operation he died of an acute coronary occlusion.

Since claudication is nothing else but angina of the leg and foot muscles, this symptom is often accompanied by angina pectoris. Over the period of years I have collected records of 61 patients who died of coronary thrombosis from 1 to 20 years after sympathectomy. The idea that angina increases after sympathectomy because a "governor" has been removed from the patient is frequently mentioned, but I have yet to see a patient whose walking ability after sympathectomy improved to such an extent that he would overload his heart. Encouraging him to walk to the point of tolerance may be prohibited by the angina pectoris, but should that be the case, the cardiac reserve is probably so poor that sympathectomy is undertaken only to prevent amputation.

An electrocardiogram taken before and after a standardized exercise, such as a two-step Master test, gives a fair idea of cardiac reserve. Our cardiologists, however, do not advise this test if the cardiogram taken at rest is abnormal. Walking up two flights of stairs in one minute is a simple, readily available test of tolerance and reveals readily whether angina pectoris or dyspnea appears earlier than claudication. Claudication as a surgical indication should here be ignored.

Renal insufficiency, revealed by an elevated preoperative nonprotein nitrogen or urea nitrogen, is a contraindication; we have not seen postoperative renal insufficiency, such as may occur after aortic resection. It is curious that a high nonprotein nitrogen on entrance may often return to normal after hydration and sedation. It has been my custom to repeat the initial blood chemistry.

General cardiovascular effects, such as decrease in cardiac output or postural hypotension with postural tachycardia, do not occur after thoracolumbar sympathectomy unless the splanchnic nerves are simultaneously removed. Since this is beyond our scope here, it will not be further discussed.

Venous thromboses and pulmonary embolism seem to occur more frequently after sympathectomy for thromboangiitis obliterans than after the operations for other forms of disease. This occurs when the lesion is subacute and smoldering and calls for a cooling-off period with sodium thiosulfate. In patients with a history or evidence of deep venous thrombosis and pulmonary embolism preoperative anticoagulant therapy with daily injections of 100 mg. for three to five days has been my practice. This is not ordinarily done in arteriosclerotic disease. While early ambulation is observed after all sympathectomies, this is not feasible if the sympathectomy is combined with amputation.

Gangrene after sympathectomy has created considerable attention and may be attributed to several factors.[8,9] If both major and collateral pathways are obstructed, diversion of blood to the thigh and lower leg may increase ischemia of the foot. Freeman and his associates[9] advanced the ingenious idea that the opening of the arteriovenous shunts reduces capillary flow to a point where failure of terminal circulation has to occur. I know of no better way of avoiding "paradox gangrene" after sympathectomy than the test for the rise of skin temperatures after paravertebral or peripheral nerve block, as pointed out earlier in this paper.

There are, however, other factors to be considered. The position of the patient on the operating table, together with constricting straps or adhesive tapes, which are placed before the table is broken, may result in undesirable pressure or may have a tourniquet effect on a poorly vascularized limb. Section of the sympathetic chain under general anesthesia frequently leads to initial vasoconstriction, which may last one or two days, before full vasodilation appears. Warren and associates[57] have abolished this effect by injecting procaine into the cut distal segment. As a result of hemorrhagic or anesthetic hypotension, a stenotic, atheromatous artery may throm-

bose, leading to massive gangrene. In spite of all these pitfalls, gangrene after sympathectomy must be very rare, and I have never seen it.

"Genitofemoral neuralgia" following lumbar sympathectomy is a complication which we used to see early in our experience in the late 20's and early 30's, appearing in about 10% of the patients and lasting from four to six weeks, and being readily controlled with codeine and acetylsalicylic acid. In the last few years this postoperative complaint has occurred in *practically every case*, and the reasons for this are not apparent. In may be that we are more aware of this complication, that the patients are tenser and more excitable than they used to be, or that a new factor has been introduced to account for this marked increase.

The *"neuralgia"* does not develop until about the 10th day after lumbar sympathectomy, and most patients have left the hospital by that time. It is much severer at night in bed, and during the day it seems to be tolerable. The pain or paresthesia is limited to the external surface of the thigh along the distribution of the lateral cutaneous nerve of the thigh, but then, again, it may radiate down to the knee, as though it had a femoral distribution. It certainly does not radiate toward the genitalia and hence could not be a true genitofemoral nerve involvement. Occasionally it has a deep, boring character.

The pain is frequently—but not always—accompanied by a cutaneous strip of hyperhidrosis, a marginal hyperhidrosis which one sees at the border of all sympathectomized nonsweating areas. This observation of Tracy and Cockett [58] suggests paravertebral blocks proximal to the removed ganglia on the basis that this is a symptom of attempted regeneration—an irritative lesion. It is very true that in thoracolumbar sympathectomies for hypertension or for causalgic states, one never sees this pain on the thigh, the pain developing at higher segments in the form of an intercostal neuralgia. I cannot say, however, that procaine blocks to the first lumbar segment, which are not easy anyway, have given the patients very much help, except temporarily.

Over the course of years, we have given many other factors our attention. Large Deaver retractors, possibly contusing the nerve on the psoas muscles, have long been eliminated. Only small Hibbs sponges have been used for retracting the psoas. The nerve itself has been scrupulously avoided. Cushing clips, which we consistently employ, have been eliminated by some members of our staff, but their avoidance has not made any difference. Procaine has been infiltrated into the proximal cut end of the chain; and the genitofemoral nerve has been flooded with it, producing no decrease of this complication.

The possibility of activating a lumbosacral arthritis by the patient's position on the table has been considered, as well as a trochanteric bursitis. But the neuralgia appears after abdominal sympathectomies, with the patient on his back, a small pillow supporting it. Every one is familiar with the backache which patients have after any length of stay on the operating table, but this neuralgia has no resemblance to the radicular pain of osteoarthritis. Nevertheless, in a few cases we have followed Pässler's [59] suggestion of manipulating the spine, with no particular improvement. In one case, the orthopedic staff injected the trochanteric bursa, but this failed to help.

Since spinal anesthesia per se leads to a certain small percentage of genitofemoral neuralgias, a series of lumbar sympathectomies have been performed under general anesthesia. No decrease of neuralgic pain was noted.

The following characteristics are important in understanding and managing this postsympathectomy neuralgia. It never occurs until 8 to 10 days after operation. In apprehensive, high-strung patients it creates fear, they believing that some vascular complication or a "paralysis" is setting in. It should be intensively treated by telling the patient at discharge (*a*) that the pain may

appear, (*b*) that it is annoying but innocuous, and (*c*) that it subsides in four to six weeks. When the 1 mg. (1000μg.) doses of cyanocobalamin came into use in thoracic surgery for intercostal neuralgia, most of us hoped that it was the solution. In my hands it has been a disappointment, although perhaps the neuralgia after both the thoracic and the lumbar sympathectomies may last a little less long.

A bedboard placed under the mattress is routinely used and may help the patient's arthritis, but not the neuralgia. The paravertebral block to the proximal, irritable segment of the chain is most logical, and we are using it in patients who lose three to four weeks of sleep, become exhausted, fail to eat, and are not relieved by salicylates, codeine, or even dihydromorphinone (Dilaudid). There is a real possibility here of producing narcotic addiction.

What I have said here about "genitofemoral" neuralgia applies to the intercostal neuralgia after thoracic sympathectomy. I have long grappled with this problem in managing hypertensive patients after splanchnicectomy. Resection of the intercostal nerve and removal of the corresponding posterior root ganglion, which we thought might have developed an apoplectic insult, were of no avail.[53] Proximal sympathetic block with a longer-lasting local anesthetic, such as lidocaine (Xylocaine) is helpful, and, generally speaking, the patients seldom develop the emotional state that follows lumbar sympathectomy.

It may be, finally, that we are now operating on more advanced types of arteriosclerosis and that ischemic posterior root ganglion or cord changes are at play. The problem still awaits solution.

Spinal cord changes after sympathectomy. There are a number of large statistics[61] to indicate that permanent spinal cord damage can be absent in as large a series as 10,000 to 30,000 spinal anesthesias. The minor sequelae, such as spinal-puncture headache, backache, or genitofemoral neuralgia, are transitory, and one can readily accept them because of the many advantages of spinal anesthesia in vascular surgery, such as complete muscular relaxation, vasomotor paralysis, absence of endotracheal tube, and many bronchopulmonary complications. For these reasons, my method of choice for all lumbar sympathectomies below the diaphragm is a spinal anesthesia, reaching to at least the sixth thoracic segment.

Recently, however, owing to shifting of responsibility from the surgeon to the anesthesiologist and as the result of training requirements of anesthesia residents, spinal anesthesia has become a cumbersome, prolonged procedure. Several mixtures of dextrose, ephedrine, and other substances are added to the procaine, and the procaine is not dissolved in the patient's own spinal fluid but is obtained from sealed ampules, which themselves need sterilization. Perhaps as a result of this, I have recently observed two patients with permanent cord damage after lumbar sympathectomy done under spinal anesthesia and have lost my nerve in continuing to use this method until it is again simplified and standardized.

Sexual changes in bilateral high lumbar sympathectomy. The fact that the contractility of the vasa deferentia, prostate, and seminal vesicles may be lost when both first lumbar sympathetic ganglia are excised has created considerable anxiety in both the patient's and the surgeon's mind. The follow-up studies of Whitelaw and Smithwick[62] have done a great deal to clarify one's concepts. From experience with 183 questionnaires turned in by patients who have had various forms of sympathectomy, it would appear that preservation of the first lumbar ganglion on one side is a good safeguard against "dry intercourse." On the other hand, bilateral lumbar sympathectomy from L-1 to L-3 on both sides resulted in permanent loss of seminal emission in 54% and temporary reduction or permanent loss of erection in 63% of the cases.

My own, far more limited experience would indicate that one can never predict

with any kind of assurance whether or not the patient will lose the seminal discharge either after splanchnic nerve section with thoracolumbar sympathectomy or after high lumbar sympathectomy.[63] It occurs, however, frequently enough to warrant its clear discussion with the patient and the preservation of one lumbar ganglion if the state of peripheral circulation permits it. The sympathectomized male does not lose the sensation of ejaculation at the time of orgasm, even though no sperm is discharged. Some secretion of mucous glands does occur. As a matter of fact, the customary lumbar sympathectomy from L-2 to L-4 has never resulted in loss of erection or loss of seminal discharge. On the contrary, a sizable number of our splanchnicectomized patients have had children after operation,* and too much dwelling on the subject may introduce a purely psychologic hazard. Arteriosclerotic patients, especially with the Leriche syndrome, have impotence in a number of instances, and the operation simply adds to their preoperative disability.

In the female, as stated from our clinic in 1949,[52] sympathectomy has no adverse effect on the genital tract. Many records are available of women who have become pregnant and have borne children. The childbirth itself may be painless until the head is engaged in the perineum, because visceral sensory nerves are interrupted when splanchnic and lumbar sympathetics are cut.

Comment

From the foregoing considerations it is obvious that sympathectomy is but one phase of treatment of the total patient. If the operation is done for *intermittent claudication,* one must be cautious in promising results, although a well-maintained collateral circulation in Grade I arteriosclerosis is the most likely to show improvement. Immediate improvement in claudication after sympathectomy in cases of low-femoral or popliteal occlusion has been reported,[43] but such has not been my experience. Patients may expect gradually increasing walking ability during the first six months to a year; since there is also spontaneous improvement in collateral circulation, especially on systematic, graded walking exercises, it is difficult to say how much effect on claudication sympathectomy has. Cold sensitivity due to ischemia is definitely lowered.

Even though the claudication distance has hardly been lengthened, the pain of claudication is definitely modified to a "tired feeling." If patients know that they cannot "hurt" themselves by walking with a mild cramp, they increase their contraction hyperemia. Walking combined with nylidrin will give the sympathectomized arteriosclerotic patient of Grade I the best possible walking distance. All this improvement can be vitiated by a sudden arterial thrombosis, a not infrequent sequence in the course of peripheral arteriosclerosis. While statistically difficult to prove, the sympathectomized limb stands such an acute vascular accident better.

Claudication in the higher grades of arteriosclerosis has not been influenced at all. Ulceration and terminal patches of gangrene respond remarkably fast to sympathectomy in thromboangiitis obliterans and other lesions exhibiting terminal vascular disease with well-maintained collateral circulation proximal to it. On the other hand, obliterative arteriosclerosis with arteriolar sclerosis responds very poorly, if at all. The hypertensive arteriolosclerotic ulcer of Martorell[64] will heal slowly if sympathectomy is combined with wide excision of the ulcer, covered by a split-thickness graft.

In the acute arterial occlusions there is no place for sympathectomy if the embolus can be aspirated or the thrombus can be reamed out. In treating the subacute or

* This, of course, is not absolute proof of fertility of the male—according to the Roman law, "Pater semper incertus."

late stages of acute arterial occlusion, however, sympathectomy does relieve rest pain and may improve circulation if patency of the main arterial pathway cannot be fully restored. Again, the protection of an ischemic limb from gangrene is the object of sympathectomy, and no clear-cut help from claudication can be expected.

A definite indication for prophylactic sympathectomy exists under the following conditions: 1. Sympathectomy of a single lower extremity is indicated if the limb is afflicted with vascular disease when the other extremity has been amputated. This principle applies especially to arteriosclerotic and diabetic patients, in whom the amputation rate of the second extremity varies from 10% to 50%. 2. Sympathectomy should be done prior to definitive surgery of aneurysms, whether the aneurysm is aortic, iliac, femoral, or popliteal. Even though the excision and graft of aneurysms are most successful, the incidence of postoperative thrombosis and minor embolic accidents is sufficiently great to justify the addition of this procedure to it. In laparotomies this prolongs the operation for not more than 5 to 10 minutes: for the extremity aneurysms, notably in the lower extremity, a sympathectomy done a week ahead or simultaneously is worth-while insurance. Inavoidable clamping of sclerotic vessels, even if heparinized, leads to a certain percentage of small thrombi, emboli, and vasospastic phenomena. 3. Sympathectomy has also been performed prior to or simultaneously with all endarterectomies and vascular grafts. One might say that this shows a certain lack of confidence in these procedures, the exact indications and limitations of which are being discussed by other members of this symposium. It is true that a real evaluation of these methods cannot be made when combined with other procedures. However, in the early vascular accidents or the late thromboses following "direct" surgery, even if they do not exceed 30% [65,66] or 70%,[67] the extremity is better prepared to meet them. 4. Sympathectomy has a real place in the treatment of diffuse arterial disease in which segmental resection, bypass, or thromboendarterectomy is futile or in cases in which the outcome is doubtful, so that a preliminary sympathectomy is advised before definitive surgery is contemplated. Such a situation exists in widespread aortic or iliofemoral stenoses or in short segmental obliterations with short, sturdy collaterals, where sympathectomy alone may increase claudication distance to a great extent. If such expectation is unfulfilled in six months to a year, a definitive approach can still be attempted.

Because we have combined sympathectomy with physical exercise, drugs, and endarterectomy and bypass procedures, its exact value is difficult to define. Since it cannot restore patency of a major artery, it can never have the effect of a carefully performed endarterectomy or a vascular graft. On the other hand, there are situations, unfortunately far too many, in which these procedures cannot be carried out or in which immediate or delayed failure of a restored circulation occurs. Such a circulation is again devoid of large functioning collaterals [42] and is in great need of a sympathectomy.

Restored main arterial pathways with good peripheral pulses do not necessarily ensure adequate muscle flow. I have seen remarkable pulsations and oscillometric curves after vascular grafts with persistent claudication. The micromesh in striated muscle or the obliteration of muscle branches is an added difficulty, and sympathectomy here will help by lower collateral resistance and delivering more blood to the terminal vascular tree.

One final consideration is the simple and the harmless character of sympathectomy. Patients in the 80's can tolerate it, and if we can devise means to eliminate postsym-

pathectomy neuralgia, it has negligible after-effects.†

Summary

Sympathectomy for occlusive peripheral vascular disease is neither the panacea which will relieve all claudication, heal all ulcers, eliminate gangrene, and prevent amputation, nor an obsolete procedure, which has been superseded by thromboendarterectomy and vascular grafts. The interruption of vasomotor impulses to an extremity has beneficial effects in stabilizing blood flow, decreasing collateral resistance, and improving cutaneous circulation, and even the circulation of the muscle under certain defined circumstances. Sympathectomy also interrupts afferent fibers, which conduct heat and cold impulses, thus adding to the comfort and safety of an ischemic limb.

There is no conflict between various surgical procedures undertaken to increase blood flow to an ischemic limb. Their point of attack differs, and their combination is often the safest and most satisfactory solution of a vascular problem.

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† Smithwick's latest contribution to evaluation of the place of sympathectomy in the treatment of obliterative vascular disease of the lower extremities[65] became available after the completion of this paper. He also emphasizes the importance of proper case selection, but the classification of his patients into 12 groups and his insistence on "flushing time" as a criterion for a successful sympathectomy do not completely agree with our experience.

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The Patella in Degenerative Joint Disease

A Clinicopathologic Study

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A detailed description of the patella in degenerative joint disease in a large series of cases has not been reported in the literature. The marked increase in the number of patellectomies for this disease in recent years has made this study possible. Young and Regan [8] published a report in 1945 which indicated that 18 patellectomies for degenerative joint disease had been performed at the Mayo Clinic up to that time. During the five-year period, 1950 through 1954, a total of 154 patellectomies for degenerative joint disease were performed by surgeons at the Mayo Clinic. The purpose of this paper is to report the changes found in the patellas and the results of a follow-up study of the patients operated on during this five-year period.

Anatomic and Pathologic Considerations

The patella is a triangular bone, the apex of which points distally, and this shape is best recognized from the anterior, or nonarticular, surface. The posterior surface is divided into an oval articular region, above, and a nonarticular apex, below, to which the infrapatellar fat pad is attached.

Goodsir [4] described seven articular facets of the patella and the manner in which they articulate with the femoral trochlea. Grossly the large lateral facet and the small medial facet are divided by a prominent longitudinal ridge. These features enable one to orient the patella, even when it is distorted by degenerative changes. As a result of the valgus alignment of the knee, there is a mechanical tendency for the patella to displace laterally when the quadriceps muscle contracts. Lateral displacement of the patella is opposed by the anterior projection of the lateral margin of the trochlea and by the adductor action of the vastus medialis muscle.[5]

The patellofemoral joint is often the first joint to show degenerative changes. Heine [6] studied the joints in 1000 routine necropsies and reported that degenerative changes, which can be seen by the naked eye, appear first in the knee during the second decade of life. Severe degenerative changes were found first in the knee joint; they occurred in the fourth decade and were commoner among women than among men. Bennett, Waine, and Bauer [1] reported changes found in the knee joint at various ages. Changes were found first in the second decade; microscopic abnormalities were most apparent over the lateral facet and vertical ridge of the patella and the exposed portions of the articular surfaces of the tibial plateaus. Wiberg [7] reported the results of an extensive radiographic study of the patellofemoral joint. In several cases of advanced degenerative joint disease, he noted lateral subluxation of the patella.

Analysis of Cases

During the five-year period, 1950 through 1954, a total of 154 patellectomies were carried out on 136 patients with degenera-

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tive disease of the patellofemoral joint. There were 85 female and 51 male patients. All patients presented with the complaint of pain. Associated complaints were locking, instability, stiffness, crepitus, and swelling. Physical findings noted were tenderness, crepitus, effusion, and limitation of motion. The histories could be divided into two groups, depending on the presence or absence of a predisposing condition. An etiologic factor was present in 89 cases (Table 1), while in the remaining 47 cases no predisposing condition was found.

There was a history of trauma in 45 cases. In 13 cases there was an old fracture of the patella, the lower end of the femur, or the upper end of the tibia. A torn semilunar cartilage was found at operation in nine patients. The remaining 23 patients gave histories of injury, but specific findings were not observed.

TABLE 1.—*Conditions Predisposing to Degenerative Disease of the Patellofemoral Joint*

Condition	Number of Patients
Trauma	45
Recurrent dislocation of patella	20
Obesity	10
Osteochondromatosis	4
Old rheumatoid arthritis	3
Bipartite patella	3
Genu valgus	1
Genu varus	1
Old poliomyelitis	1
Osteochondritis dissecans	1
Total	89

A history of recurrent dislocation of the patella was given by 20 patients, of whom 18 were female and 2 were male patients. In nine cases dislocation was bilateral; all nine patients were female. These patients complained of pain and instability or dislocation. The youngest patient was 15 years of age and the oldest 58 years of age; the average age was 35.

The height and weight of 88 patients were recorded with the physical examination. These were compared with normal standards for men and women.[3] Seventy-two patients were 30 lb. or more overweight; in ten of these patients (Table 1) no other condition predisposed to degenerative joint disease.

TABLE 2.—*Grading of 119 Patellas in 109 * Patients*

Grade	Number of Patellas	Number and Sex of Patients	
		Male	Female
1	28	10	16
2	58	25	29
3	33	6	23
Total	119	41	68

* Both patellas were removed from 10 patients.

Pathologic Anatomy

The patellas were available in 109 cases; in 10 patients both patellas were removed, making a total of 119 patellas examined. Each patella was anatomically oriented and inspected for the presence of cartilage degeneration, eburnation of the articular surface, and marginal hyperplasia. The bone was then sectioned horizontally through the center so that a cross section of the vertical ridge was obtained. The patellas were divided into three grades by means of the following criteria: Grade 1, cartilage degeneration with absence of or slight marginal hyperplasia; Grade 2, cartilage degeneration with well-marked marginal hyperplasia; Grade 3, gross distortion in the shape of the patella, with eburnation of the articular surface (Table 2). This method of grading is rather simple, and represents the progression of degenerative changes.[2]

Patellar Degeneration, Grade 1.—The patellas were grouped according to the region of articular cartilage most involved by the process of degeneration (Table 3). Fibrillation of the cartilage is characteristic in the early stages of degeneration (Fig. 1). A predisposing condition was present

TABLE 3.—*Patellar Degeneration, Grade 1*

Main Site of Degeneration	Number of Patellas	Number and Sex of Patients		Predisposing Conditions	
		Male	Female	Trauma	Recurrent Lateral Dislocation
Medial facet	8	2	6	6	0
Lateral facet	5	1	3	3	1
Vertical ridge	15	7	7	5	5
Total	28 *	10	16	14	6

* Both patellas were removed from two patients.

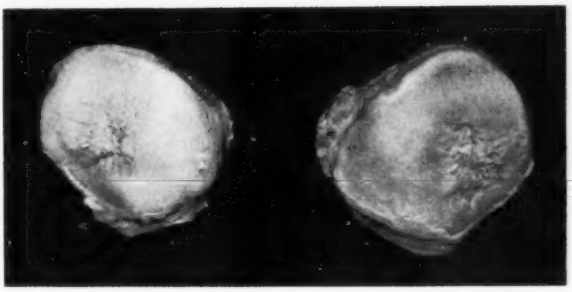

Fig. 1.—(*a*) Patella of a 19-year-old woman who complained of giving way of the knee and pain. There is marked fibrillation of the midportion of the lateral facet. (*b*) Patella of a 39-year-old woman who injured her knee four years prior to operation. A tear of the anterior portion of the lateral meniscus was found. Fibrillation of the lateral facet is noted.

in 20 of the 26 patients. The articular cartilage of the vertical ridge was most frequently degenerated, while that of the lateral facet was the least often affected. Trauma may injure any part of the articular surface of the patella. In recurrent lateral dislocation, the vertical ridge and lateral facet are damaged.

TABLE 4.—*Patellar Degeneration, Grade 2*

Main Site of Degeneration	Number of Patellas	Number and Sex of Patients		Predisposing Conditions			
		Male	Female	Trauma	Recurrent Lateral Dislocation	Others	
Medial facet	13	8	5	7	0	Osteochondromatosis	1
Lateral facet	9	2	6	2	2	Obesity	2
Vertical ridge	36	15	18	10	3	Old rheumatoid arthritis	2
						Obesity	2
						Bipartite patella	1
						Osteochondromatosis	1
Total	58 *	25	29	19	5		9

* Both patellas were removed from four patients.

Patellar Degeneration, Grade 2.—The patellas were grouped in the same manner as those in Grade 1 (Table 4). As degeneration progresses, the cartilage becomes thin and granular, with a yellow-brown discoloration, and the articular surface is more diffusely involved. Marginal hyperplasia usually begins at the inferomedial margin of the articular surface, and eventually there may be circumferential lipping. There was a predisposing condition in 33 of the 54 cases, trauma being most frequent. The vertical ridge was the most frequent site of degeneration (Fig. 2).

Patellar Degeneration, Grade 3.—The patellas were grouped according to the site

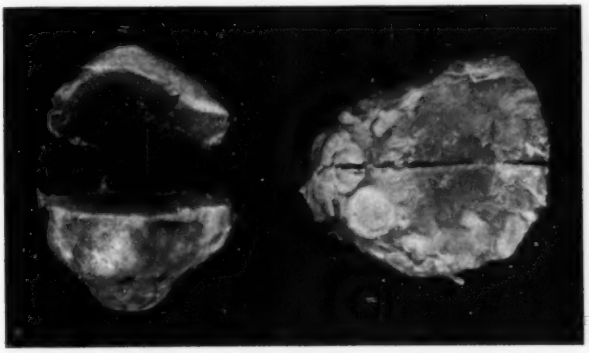

Fig. 2.—(*a*) Patella of a 44-year-old woman who had recurrent lateral dislocation of the patella. Degeneration of the cartilage is most marked over the vertical ridge, and there is marginal hyperplasia inferomedially. (*b*) Patella of a 44-year-old woman who had painful knees but no history of trauma or dislocation. There is marked degeneration of the cartilage of the lateral facet with circumferential marginal hyperplasia, which is somewhat nodular medially. This patella was subluxated laterally on the roentgenogram and appears to be an early form of the type of patella shown in Figure 3.

TABLE 5.—*Patellar Degeneration, Grade 3*

Site of Eburnation	Number of Patellas	Number and Sex of Patients		Predisposing Conditions			
		Male	Female	Trauma	Recurrent Lateral Dislocation	Others	
Medial facet	2	2	0	1	0	Osteochondromatosis	1
Lateral facet	28	4	21	0	4	Obesity	5
						Genu valgus	1
						Osteochondromatosis	1
						Old rheumatoid arthritis	1
Total surface	3	0	2	0	1	Old rheumatoid arthritis	1
Total	33 *	6	23	1	5		10

* Both patellas were removed from four patients.

of eburnation of the articular surface (Table 5). Eburnation refers to the polished, mirror-like surface of denuded subchondral bone and is a late manifestation of degeneration. Predisposing conditions existed in 16 of the 29 cases, of which lateral dislocation and obesity were most frequent.

There were two patellas with eburnation of the medial facet. One was removed from a 61-year-old man with osteochondromatosis; the other, from a 37-year-old man with an old fracture of the patella.

There were three patellas with eburnation of the whole articular surface; two were removed from a 42-year-old woman with a history of recurrent lateral dislocation; the other, from a 63-year-old woman with a history of old rheumatoid arthritis. The tangential patellar roentgenogram in the latter case showed marked lateral subluxation of the patella.

There were 28 patellas with eburnation of the lateral facet, all of which presented a characteristic appearance (Fig. 3). The lateral facet is cupped out between the vertical ridge, medially, and a hyperplastic rim of bone, laterally. The medial facet is covered by degenerated articular cartilage. A cross section has a typical comma-shaped appearance. These features indicate that the patella is displaced laterally in its articulation with the femoral trochlea. Tangential patellar roentgenograms were available in three cases, and in each the patella was subluxated laterally (Fig. 4). The histories were remarkably similar in that there was a preponderance of females (88%) of the same age group (average age, 58 years) with no history of trauma. There was a history of recurring lateral dislocation in four cases (16%).

Follow-Up Study

Because operation was performed to relieve pain, it was felt that the patient's own evaluation was important, and that a follow-up study by letter would be worth while. The follow-up period was from two to seven years. We thought it would

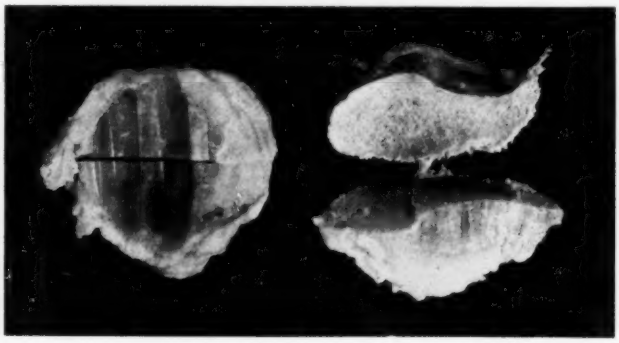

Fig. 3.—Left and right patellas removed from a 55-year-old woman with painful knees but no history of trauma or dislocation. The appearance is characteristic of patellas with eburnation of the lateral facet.

Fig. 4.—Lateral displacement of the patella of a 54-year-old woman with a painful knee and no history of trauma or lateral dislocation of the patella. The patella showed eburnation of the lateral facet.

be interesting to compare the results of surgical procedures with the grade of degeneration of the patella, and the only patients evaluated were those whose patellas were examined. The results are summarized in Table 6.

The over-all response was 68%. In general, the patients were well satisfied with the results of surgical measures. Only one patient was made worse; postoperative infection developed, with resultant ankylosis of the knee. Pain, when present after operation, was often slight and was not a real handicap to the patient. It is interesting to note that patients who had patellar degeneration of Grade 3 were the most satisfied group. More patients in this group responded to follow-up inquiries (79%), and absence of pain was reported in a higher percentage of cases (61%). The knee operated on was better than its mate in 29% and was the same in 52%, probably indicating that both knees are often involved in advanced cases of degenerative joint disease.

TABLE 6.—*Patellectomy for Degenerative Joint Disease: Percentage Evaluation of Follow-Up Response in Relation to Grade of Degeneration*

Grade of Degeneration	Follow-Up Study		Condition Improved	Absence of Pain	Range of Motion		Comparison of Operated Knee with Its Mate	
	Patients	Per Cent			Full Extension	90-Degree Flexion	Better	Same *
1	18 of 26	69	78	39	100	100	12	17
2	33 of 54	61	88	42	76	82	17	10
3	23 of 29	79	87	61	96	92	29	52
All grades	74 of 109	68	83	47	91	91	19	26

* Does not apply to bilateral cases.

Comment

Degenerative disease of the patellofemoral joint is commoner among women than among men. In seeking an explanation for this, the known etiologic factors must be examined. The three most frequent conditions predisposing to degenerative disease of the patellofemoral joint are trauma, obesity, and recurrent lateral dislocation of the patella.

Trauma is commoner among men, and this explains the higher incidence of male patients having degeneration of Grades 1 and 2 than degeneration of Grade 3. The relative absence of trauma among patients having Grade 3 degeneration probably reflects earlier surgical intervention in cases in which trauma was a predisposing factor. It is interesting to note that the incidence of overweight of 30 lb. or more was approximately the same for men (7 of 30, or 23%) as for women (15 of 58, or 26%) with degenerative disease of the patellofemoral joint, since this condition is generally thought to be commoner among women.

Recurrent lateral dislocation of the patella is commoner among women, and it has been shown that dysplasia of the lateral margin of the trochlea, and of the patella itself, is frequently present in these cases.[7] Lateral subluxation of the patella frequently occurs in advanced degenerative joint disease, and is commoner among women. There are two possible explanations for this. First, the condition may be analogous to that of the hip joint, where mild degrees of dysplasia result in early wearing out of the joint. Second, it may be that in women there is a mechanical predisposition to lateral displacement of the patella, and subsequent degenerative disease, which is the result of the greater degree of valgus alignment of the knee normally present. The integrity of the vastus medialis muscle is important, for weakness and atrophy of this muscle permit lateral displacement of the patella during movement of the knee. Indeed, there may

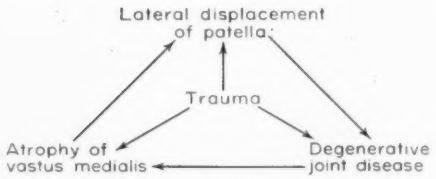

Fig. 5.—Vicious cycle in the evolution of degenerative disease of the patellofemoral joint.

be a vicious cycle whereby atrophy of the vastus medialis permits lateral displacement of the patella, which gives rise to degenerative changes, which cause pain, disuse, and further atrophy of that muscle. Trauma may play an initial or aggravating role in this cycle (Fig. 5).

Summary

The cases of 136 patients who underwent patellectomy for degenerative joint disease were reviewed, and 119 patellas from 109 of these patients were examined and graded according to the degree of degenerative change.

Advanced degenerative disease of the patellofemoral joint is commoner among women than among men. The patellas of these patients are worn out on the lateral side and have a characteristic appearance.

The higher incidence among women is probably the result of increased tendency for the patella to displace laterally, either from dysplasia of the joint or from the more acute valgus alignment of the knee in women.

Patellectomy for degenerative joint disease gives subjective improvement in a high proportion of patients, particularly those with advanced disease.

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Significance of Peroperative Cholangiography in the Management of Gallbladder Disease

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The therapeutic significance of peroperative cholangiography is still a matter of dispute, major objections to its application being the high frequency of diagnostic difficulties and incorrect interpretations and the amount of delay caused during the operation.

Before proceeding to a discussion of our own results, it may be useful to include a brief description of the type of cholangiography routinely performed in the course of cholecystectomy for gallbladder disease at the surgical department of St. Canisius Hospital.

Technique of Peroperative Cholangiography

The patient on the operating table is placed on a flat cassette tunnel so as to facilitate insertion of an x-ray plate with Lisholm screen at the level of the area of operation.

After opening of the abdominal cavity and exploratory examination of the gallbladder and surrounding abdominal organs, the biliary tree is carefully dissected and the cystic duct ligated as far proximal as possible to the gallbladder. Through a small, transverse incision a lightly curved, bulb-tipped needle is inserted into the cystic duct and fixed in position by means of a second, more proximally located, ligature. Only after bile has started to flow from the needle is the syringe, filled with contrast medium, fitted to the needle (all air having duly been removed) and the contrast medium injected into the biliary system.

This procedure is essential inasmuch as it prevents the introduction of air bubbles and so incorrect interpretation of the roentgenogram. For the same reason, it must be considered inadvisable to inject the fluid via a catheter introduced into one of the biliary ducts, as some authors recommend. If bile does not start flowing from the bulb-tipped needle spontaneously, it is recommended that the cystic duct be explored for the presence of calculi or calculous deposits.

The type of contrast medium used, too, is vital if the maximum profit is to be derived from this method. A water-soluble type of contrast medium is to be preferred, since the slight viscosity of the substance renders it possible to inject quickly, while, on the other hand, the fluid mixes readily with the bile. Experience has tended to show that some 20 ml. of a 35% solution of Dijodon (identical with iodopyracet) is a perfectly harmless fluid which mixes well with bile and provides an excellent contrast, without undue risk of calculi being obscured. In agreement with the findings of other workers, including Swedberg, 1952, and Pop, 1952, we have never been able to observe any injurious effects.

If, at a relatively early stage, injection should prove possible only with the application of pressure, it is prudent to check on the possibility of a wrong (i. e., subserous) position of the needle or of a cystic duct obstruction, caused either by stricture or by an accumulation of stones. It is desirable, furthermore, not to inject the contrast fluid too quickly, since in the

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presence of a spastic (reflex type) condition of Oddi's sphincter an abnormal dilatation of the biliary ducts may be simulated. If necessary, injection should be achieved in two stages in such cases. At the same time, momentary hyperventilation (to produce a period of apnea) may do much to improve radiographic definition and so contribute toward a correct interpretation of the roentgenogram, while it is necessary, furthermore, for the purpose of radiography, to project the bile ducts clear of the spinal column by slightly raising the left half of the thorax (Partington and Sachs, 1948).

Provided there is good cooperation among members of the x-ray department, it should be possible to have a roentgenogram developed and ready for examination within the space of five minutes. After removal of common bile duct calculi, the prudent course is to have a control cholangiogram made in order to make sure that no stones have remained behind (Pirkey et al., 1953; Mixter et al., 1951). The presence of such an eventuality should be considered (*a*) if, owing to too forceful injection of the contrast medium, a few of the calculi have been forced into the minor intrahepatic bile ducts, (*b*) if a calculus has become embedded in the wall of a duct (Kantor and associates, 1955), or (*c*) if contrast fluid of too high concentration has been used (Rieben, 1952).

Cholangiographic Interpretation

Interpretation of the cholangiogram should be less speculative in character as more experience is gained and as one slowly becomes familiar with the picture of normal bile ducts visualized in this way, as well as with the changes produced by calculi, air bubbles, and strictures of various types.

The width of a normal common bile duct should not be in excess of 1 cm. (Pop, 1952), it being understood, however, that this standard should not be too rigidly applied, since actually spastic factors (occasionally reflex type in nature) and anatomical variations may have a considerable influence on the dimensions as visualized on the roentgenogram. Occasionally bile ducts are encountered of a width not exceeding 3 mm. (Cole and Harridge, 1956). A detailed description of the contrast image of the normal biliary system has been provided by van der Zwaag in 1951.

Spastic conditions of Oddi's sphincter are more frequently observed in cholangiography *during* than *after* the operation, probably owing to manipulations in the area of operation. The administration of morphine, too, as a preoperative measure has not infrequently given rise to spasms of Oddi's sphincter. It is consequently advisable to administer a combination of meperidine (pethidine) and atropine sulfate.

Angular negative shadows, unexpected (concave) obstruction, a bubble completely hemmed in by contrast fluid, all point to the presence of calculi. Negative shadows due to pancreatic nodules and lymph nodes give the impression of forming an integral whole with the wall and do not shift place after repeated radiographic exposures and changes in the patient's position. In exceptional cases a filling defect of the common bile duct wall is ascribable to an injury, inflammation, or congenital constriction. Such a projection may have a depth of a few centimeters.

Provided the cholangiogram is made with the necessary care, the introduction of air into the biliary system may be avoided. It is, however, important to know that negative shadows caused by air bubbles are round or oval in shape, present no irregularities of contour, and are subject to changes, of both form and place, in the event of repeated radiographic exposures and shifts of position.

Obstruction of a passage due to spasm of Oddi's sphincter causes a pencil-point type of constriction at the place where the common bile duct passes into the intestine, a constriction which may be usually elimi-

nated by repeated injection of contrast medium.

The presence of pancreatitis may give rise to a similar picture. This affection, as are also a number of other pathological changes of the surrounding organs which may all cause stricture of the bile ducts, is usually discovered on first inspection of the abdominal organs after opening of the abdominal cavity. A discussion of these changes, and that of the abnormalities of the papilla of Vater ascribable to sclerosis, tumors, or various types of dyskinesia, fall outside the scope of the present article.

Personal Data

Encouraged by the favorable results as mentioned in the literature in recent years, we have, at the St. Canisius Hospital, adopted peroperative cholangiography as a matter of routine. Results obtained in the last series of cholecystectomies for gallbladder disease seem to confirm the generally accepted trends, but have also provided a few supplementary data. Whenever this was thought desirable, a comparison has been made with a series of 100 patients in whom the gallbladder was removed without the assistance of preoperative cholangiography.

The series of patients was composed of 20 men and 80 women, with ages varying from 27 to 88 years (average, 52 years). The control series consisted of 13 men and 87 women, with ages ranging from 17 to 80 years (average age 54 years).

Conventional indications for exploratory examination of the biliary system (as indicated by Lahey) were present in the first series in 64 cases. Peroperative cholangiography demonstrated negative shadows in 19 cases, in 3 of which the shadows from the start were suspected to be ascribable to air bubbles.

Occlusion of the papilla of Vater appeared on roentgenographic evidence to be present in 10 cases and was confirmed by exploration in 8 cases; in 16 instances the duodenum did not fill with contrast medium after a single injection; after a second injection no filling was observed in 12 cases. In eight patients this appeared to be due to the presence of a calculus in the papilla. In the remaning four cases no pathological changes or calculi were found.

In 37 cases there was a history of jaundice or jaundice was established on physical examination. In 15 of these cases roentgenograms of the opacified area revealed negative shadows (probably caused by calculi); in the course of the ensuing choledochotomy stones were actually found.

It appears from these data that unnecessary exploration of the bile ducts was prevented in 40 cases, so that drainage of the common bile duct could be avoided and, consequently, the risk of complications reduced and the time of hospitalization shortened. In four cases exploration did not yield any results; in three of these cases the presence of air bubbles had previously been suspected. Highly noteworthy, furthermore, is the fact that on five occasions no indications for choledochotomy had appeared to be present, whereas the cholangiogram revealed negative shadows caused by stones and, on exploration, stones were found.

This experience alone would seem to be sufficient justification for the routine performance of contrast roentgenography during cholecystectomy.

In Table 1 the results are reviewed in more detail.

T-drainage was resorted to in 16 cases. In 17 cases—and this in spite of negative

TABLE 1.—*Survey of the Results of Cholangiography During Operation*

Indications for Exploration of Bile Ducts	No.	Positive Results: Cholangiography	Positive Results: Exploration
Conventional indication(s) without jaundice	27	5	4
Jaundice alone	20	5	4
Conventional indication(s) with jaundice	17	9	7
Total number	64	19	15
No indication for exploration	36	5	5
Total number	100	24	20

TABLE 2.—*Indications for Exploration in One Hundred Control Patients*

Indication(s) for Exploration in 100 Control Patients	Number	Exploration	Positive Result	Unnecessary Exploration
Conventional indication(s) without jaundice	32	26	12	14
Jaundice alone	12	12	5	7
Conventional indication(s) with jaundice	12	12	10	2
Total no.	56	50	27	23

results during cholangiography—an exploration was made via the cystic duct; no calculi were found. Twice a stone escaped detection, in both cases on account of its being localized in a diverticulum just in front of the papilla of Vater, the peroperative cholangiogram in this instance having failed to reveal it.

In 56 of the 100 control patients under review there were indications for exploration of the common bile duct.

Choledochotomy was performed in 50 cases, calculi being found and removed in 27 cases. T-drainage was resorted to in 48 cases; a further operation was (insofar as is known) indicated in 3 instances. Tables 2 and 3 provide a clear survey of the differences specified. The figures do not require further elucidation.

Comment

Contrary to opinions expressed in recent publications, peroperative cholangiography is considered a reliable diagnostic aid, among other things, in establishing the presence of calculi in the bile ducts. This reliability may be increased by an adequate technique and sufficient experience in the interpretation of roentgenograms.

By the use of this technique, unnecessary exploration of the biliary duct system may frequently be avoided, with the result that drainage of the common bile duct is necessary in only a small percentage of cases and the risk of postoperative complications is reduced. Both factors are, among other things, expressed in a reduction of the number of postoperative hospital days.

Conventional indications for exploration of the extrahepatic biliary duct system appear in a considerable number of cases not to be in agreement with the actual condition, which may virtually always be established by cholangiography.

Absence of indications for choledochotomy does not exclude the presence of biliary calculi, as could clearly be demonstrated by cholangiography in a few patients. Postoperative complaints may be partially prevented in this manner.

The use of peroperative cholangiography is recommended in all operations performed on the basis of suspected gallstones or biliary obstruction, hypersensitivity to iodine or the patient's precarious condition being among the only reasons for abandoning this type of examination.

Many workers (including Hicken, Kantor, Johnston, etc.) point out that bile duct exploration by means of sounds or spoons is by no means infallible as a method of detecting calculi and, consequently, should be considered inferior to cholangiography.

A certain proportion of allegedly "newly formed stones" must probably be accounted for as being missed calculi of previous operations. In this connection, mention has already been made of those bile duct stones which had seemed not to provide an indication for surgical exploration.

It is noteworthy, furthermore, that precisely those publications which mention a

TABLE 3.—*Comparison of Cholecystectomy With and Without Cholangiography*

	No.	Indication for Exploration	Exploration	T-Drainage	Unnecessary Exploration
Cholecystectomy without peroperative cholangiography	100	56	50	48	23
Cholecystectomy with peroperative cholangiography	100	64	19	16	4

fairly high percentage of negative results of explorations following suspect cholangiograms do recommend the use of a catheter in injecting the contrast medium, a method which may easily lead to the introduction of air bubbles into the biliary system. From our data it is evident how relatively easily this inadvertent introduction of air may be prevented, so that this contingency may justifiably be counted among the avoidable technical imperfections.

St. Canisius-Ziekenhuis, St. Annastraat 289.

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Effect of Thoracotomy on White Blood Cell Count

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Our interest in changes in white blood cell counts during thoracotomy was stimulated by the report of Bierman[2] in which he stated that the pulmonary artery blood contained more white cells, particularly of the polymorphonuclear leukocyte series, than did the peripheral blood. In July, 1954, we began drawing blood from the pulmonary artery during pulmonary resections after the artery was isolated but before the branches were ligated. A high white cell count, over three times the preoperative count, was found, predominantly in the granulocytic series. When simultaneous counts were made on peripheral blood, either arterial or venous, they were found to be elevated to the same degree and also had this marked left shift. The present paper is a summary of our investigations conducted at the Central Washington Tuberculosis Hospital in over 75 thoracotomies.

Material and Method

First Group.—During 50 consecutive pulmonary resections, peripheral blood was drawn preoperatively and at hourly intervals from intubation to closing of the chest (an average of three and one-half hours), then two hours after the patient was returned to the floor (two and one-half hours after the chest was closed) and, again, on the first postoperative day. Total white and differential cell counts were run on each of these samples. By multiplying the total count by the percentage of each type of cell (differential) the actual count of each type of cell is obtained. There were 30 men and 20 women in this group of patients. Two women died, one on the fifth and the other on the ninth postoperative day, both as a result of a nonspecific pneumonitis. One of these women had the highest white cell count we have seen in the entire group—65,000 per cubic millimeter. In this series the right chest was entered 23 times and the left chest 27 times. A variety of resections was done, including segmental resection, lobectomy, and pneumonectomy, or a combination of resections, such as that of one or more segments from each lobe. The type of procedure did not vary the response so long as the patient was intubated longer than two hours. The response did not vary between the sexes, nor did the side of the chest opened make a difference.

Graph 1 is a composite average of the total white blood cell count and its component parts taken from these first 50 resections. The heavy top line shows the total white blood cell count, starting at a preoperative level of 9389 and reaching a maximum of 32,060 (an increase of 3.4 times); two hours postoperatively the count has fallen to 19,637 (a decrease of 39% from the maximum response); by the first postoperative day there has been a further decrease to 14,583, or 55% below the maximum response but still 1.5 times the preoperative level. The area between the heavy top line and the first shaded area represents polymorphonuclear leukocytes—preoperatively there were 5601, increasing 3.9 times, to 21,980, at the time of maximum response and falling to 13,894 (a decrease of 37%) two hours postoperatively. On the first postoperative day there was a count of 10,492, a decrease of 52% from the maximum response but an increase of 1.9 times the preoperative level. The upper shaded area represents the band forms of granulocytes, averaging 86 preoperatively, then increasing

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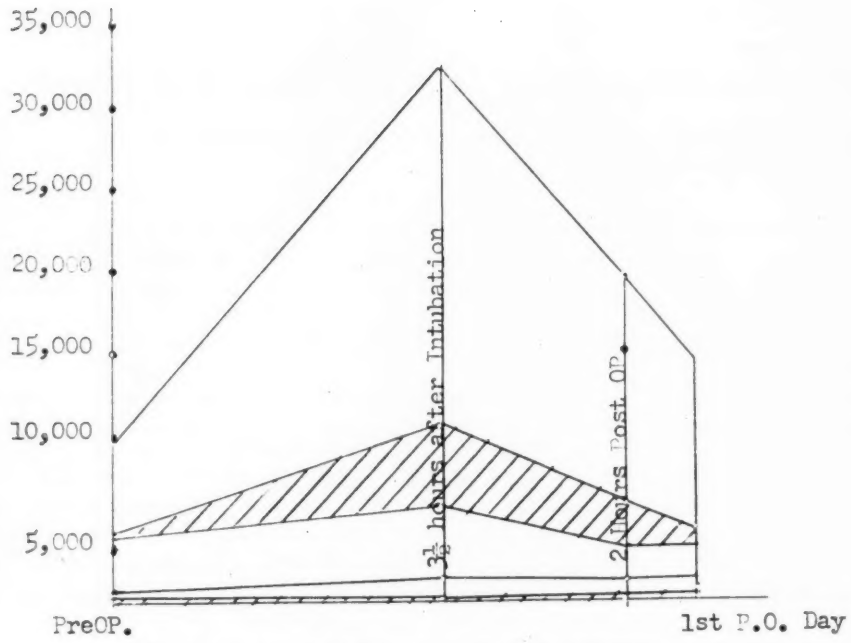


Graph 1.—Average white cell response for 50 thoracotomies.

55 times, to 4753. Two hours postoperatively there was a decrease of 38% from the maximum response, to 2945. On the first postoperative day the count was 1132, a decrease of 76% from the maximum response but an increase of 13 times the preoperative level. The increase in the white blood cell count and the marked left shift were seen in all patients, whereas the changes in eosinophil, lymphocyte, and monocyte counts became obvious only when this series of cases was averaged. The lymphocytes are represented by the area between the band forms (upper shaded area) and the heavy line just above the base line. Preoperatively there were 3121 lymphocytes, increasing to 4373 (1.4 times) at time of maximum response. By two hours after operation the count has decreased 58% from the maximum response, to 1863. On the first postoperative day there were 1999, a decrease of 55% from the maximum response and a decrease of 36% from the preoperative level. The monocytes are represented by the area between the heavy line and the small shaded area just above the base line. Preoperatively there were 306 monocytes, increasing 2.6 times to 793 at the time of maximum response. Two hours postoperatively there was a decrease of 15%, to 675, from the time of maximum response. On the first postoperative day there were 621, a decrease of 22% from the maximum response but twice the preoperative level. Eosinophils are represented by the small shaded area just above the base line. There were 275 preoperatively, decreasing 42%, to 161, at the time of maximum response, and then increasing to 260 two hours after operation. On the first postoperative day there were 339 eosinophils. This change in the eosinophil count was suspected, because in many patients eosinophils could not be found in peripheral blood at the time of maximum response. Osgood[13] reports that only a small percentage of maturated cells are in circulation at one time. The increase of 22,671 cells in every cubic millimeter of blood represents a response of over 120,000,000,000 cells in

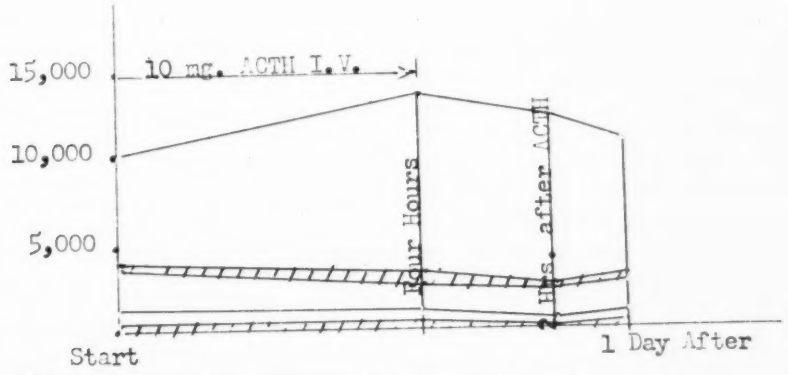
a 70 kg. man. Since most of these cells are in the granulocytic series, and it takes 2,000,000,000 cells to equal 1 gm., over 60 gm. of these cells were released into and removed from the peripheral circulation within 24 hours.

Second Group.—To determine whether or not this response is due to a rapid manufacture of cells, bone-marrow aspirations were done on 14 patients at the time of intubation and again one-half hour after the chest was closed. Two hundred cells were counted in both aspirated marrow specimens, and there was no significant change. Peripheral blood was drawn at the same time and white cell and differential counts were made to be sure that each of these patients had the typical response. Craddock et al.[7] find that it takes four days for the marrow to show response when the leukocytes have been removed at a maximum rate.

Third Group.—In order to show further that this response is not due to increased bone marrow activity, reticulocyte counts were made at the beginning of surgery and again just before closing, along with white cell and differential counts. There was no significant change in the reticulocyte counts of 10 patients.

Fourth Group.—The white blood cell response after intubation and thoracotomy are somewhat similar to those described from stress. To compare the effects of thoracotomy and stress, white cell and differential counts were done on five patients every hour during thoracotomy, and then three to four weeks later these five patients were given 10 mg. of corticotropin in 500 cc. of isotonic saline intravenously over a four-hour period. White cell and differential counts were done at the time the corticotropin was started, hourly until the intravenous infusion was completed, and again two hours after the intravenous infusion was discontinued. Another count was done the following morning.

Graph 2 represents the average of the total white blood cell count and its component parts of five patients who received 10 mg. of corticotropin intravenously in 500 cc. of isotonic saline over a four-hour period. The heavy top line represents the total white blood cell count, starting at 10,374 and reaching a maximum of 14,159 (an increase of 1.3 times); two hours after the intravenous infusion was stopped the count was 13,197, a decrease of only 7% from the maximum. The day following corticotropin the white cell count had decreased 19% from the maximum, to 11,584; this is an increase of 1.1 times the pre-corticotropin level. The area between the heavy top line and the small shaded area represents the polymorphonuclear leukocytes—before corticotropin there were 6,669, increasing 1.6 times, to 11,049, at time of maximum response and falling to 10,548

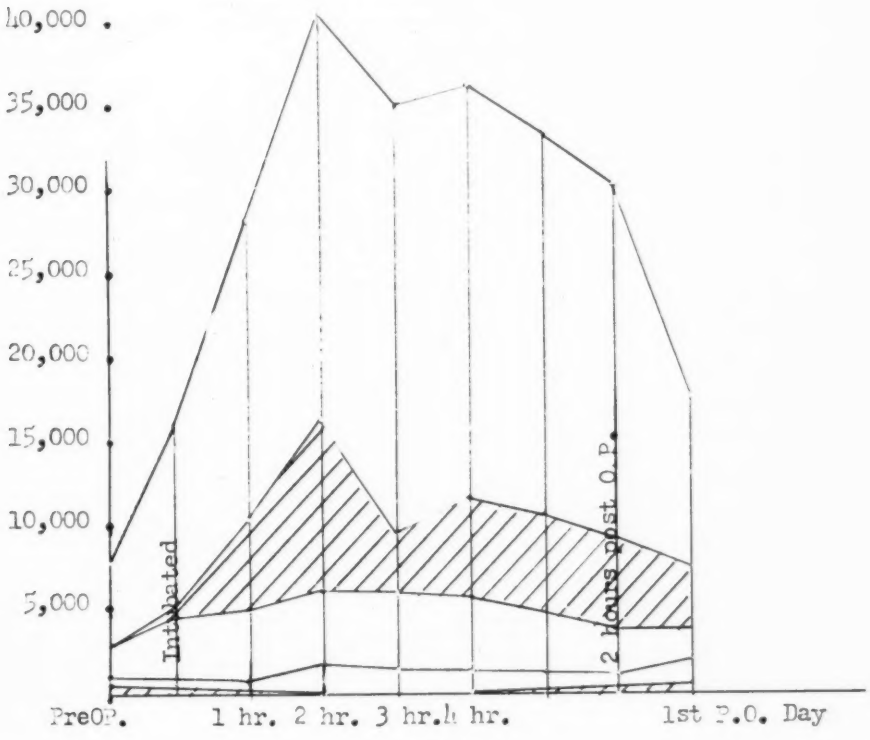


Graph 2.—Average white cell response for five cases: 10 mg. of corticotropin intravenously in 500 cc. isotonic saline over a four-hour period.

(a decrease of 5%) two hours after intravenous infusion was stopped. On the day following corticotropin there were 8625, a decrease of 12% from the maximum but an increase of 1.2 times the precorticotropin level. The upper shaded area represents the band forms of granulocytes, averaging 112 before corticotropin, and increasing 5.6 times, to 631, at the time of maximum response. Two hours after corticotropin was stopped there was a decrease of 33% from the maximum response, to 425. The day following corticotropin the count was 297, a decrease of 53% from the maximum but an increase of 2.6 times the precorticotropin level. The lymphocytes are represented by the area between the band forms (upper shaded area) and the heavy line just above the base line. Before corticotropin there were 2441 lymphocytes, decreasing 35%, to 1606, at time of maximum response. Two hours after intravenous administration was discontinued the count has increased 1.1 times that of maximum response, to 1740. The day following corticotropin there were 2120, an increase of 1.3 times the maximum response but 13% less than before corticotropin. Monocytes are represented by the area between the heavy line and the small shaded area just above the base line. Before corticotropin there were 754 monocytes, decreasing 40%, to 452, at time of maximum response. Two hours after corticotropin there was a decrease of 24%, to 346, from the maximum. On the day following corticotropin there were 267, a decrease of 41% from the maximum response but a decrease of 65% from the precorticotropin level. Eosinophils are represented by the small shaded area just above the base line. There were 398 before corticotropin, increasing slightly to 421 at time of maximum response, then decreasing 68%, to 138, two hours after intravenous infusion was stopped. On the day following corticotropin there were 275, a decrease of 35% from maximum response and 31% below the precorticotropin level. The 68% decrease of eosinophils is well within normal limits reported by Thorn et al.[11] in patients with intact adrenal cortex. A dose of 20 to 25 mg. of corticotropin intravenously in an eight-hour period is considered to be maximum stimulation. Measurement of 17-hydroxycorticosteroid excretion during surgical procedures places thoracotomy with the maximum amount [15]; therefore it represents the maximum response to stress and the 10 mg. of corticotropin given in four hours is the most that the body can respond to during the four-hour period. When we compare Graphs 1 and 2, the increase in total white cell count, the increase in polymorphonuclear leukocytes, and the left shift are similar, but the magnitude of change with thoracotomy is over twice as great. There is a similarity in the decrease in number of eosinophils and lymphocytes. The monocytes decrease with corticotropin but increase with thoracotomy, and this is the first time a quick rise in monocytes has ever been reported. On the first postoperative day and on the day following corticotropin the counts are very similar, so that the increase in white blood cell count and the left shift at this time may be due to the stress of surgery.

Fifth Group.—Four patients have had pneumonectomies, three left and one right, followed by thoracoplasty three weeks later. In order to demonstrate the fact that the white cell count increased more slowly after thoracoplasty than after thoracotomy, the following case is presented:

CASE 1.—A 27-year-old white woman had a left pneumonectomy on May 13, 1955. The maximum white cell response, of 41,200 per cubic millimeter, occurred 3 hours 10 minutes after intubation. At time of closure, two hours later, the count had fallen to 37,300. This fall of 3900 cells is a common occurrence after prolonged intubation, appearing in 12 patients intubated longer than three and one-half hours. Graph 3 shows her white blood cell response, and Table 1 shows the number and type of cells at hourly intervals. The increase in the cell count and the left shift in the differential count from the preoperative count, done from one to three days before surgery, to the count at the time of intubation is quite constant. The magnitude and type of shift are similar to those shown in Graph 2 following corticotropin,



Graph 3

probably representing the response to the mental and physical strain in preparing for major surgery. This may be another reason why patients with planned surgical procedures do better than when the same procedure is done as an emergency measure. On June 13 a seven-rib thoracoplasty was done to fill the space. Graph 4 shows this response at hourly intervals, and Table 2 gives the actual number of each type of cell. When we compare the white cell response to thoracoplasty with the white cell response to pneumonectomy, we find a lag of at least an hour, and at the end of three hours after thoracoplasty there were only 29,500 cells, as compared with 41,200 cells after pneumonectomy. This may be due to the fact that when thoracoplasty was done there remained only the right lung, or 60%, of the main reservoir for the granulocytic series, which is supposed to be the lungs.

Comparison of the thoracoplasties, corticotropin administration, and thoracotomies shows that the types of response are very similar, with an increase in total white cell count, an increase in the granulocytic series with a left shift, and a decrease in eosin-

TABLE 1.—*White Cell Response to Pneumonectomy*

					Postoperative			
	Preop.	Intubated	1 Hr.	2 Hr.	3 Hr.	4 Hr.	2 Hr.	1 Day
Total count	7,900	15,800	28,500	41,200	35,800	37,300	31,200	18,000
Leukocytes	4,977	10,744	18,240	24,720	26,134	25,364	21,528	10,260
Band forms	158	632	5,415	10,300	4,654	5,968	5,928	3,960
Lymphocytes	1,975	3,742	4,275	4,532	3,580	4,476	2,496	1,440
Monocytes	553	316	285	1,648	1,432	1,492	936	1,980
Eosinophils	158	316	285				312	360

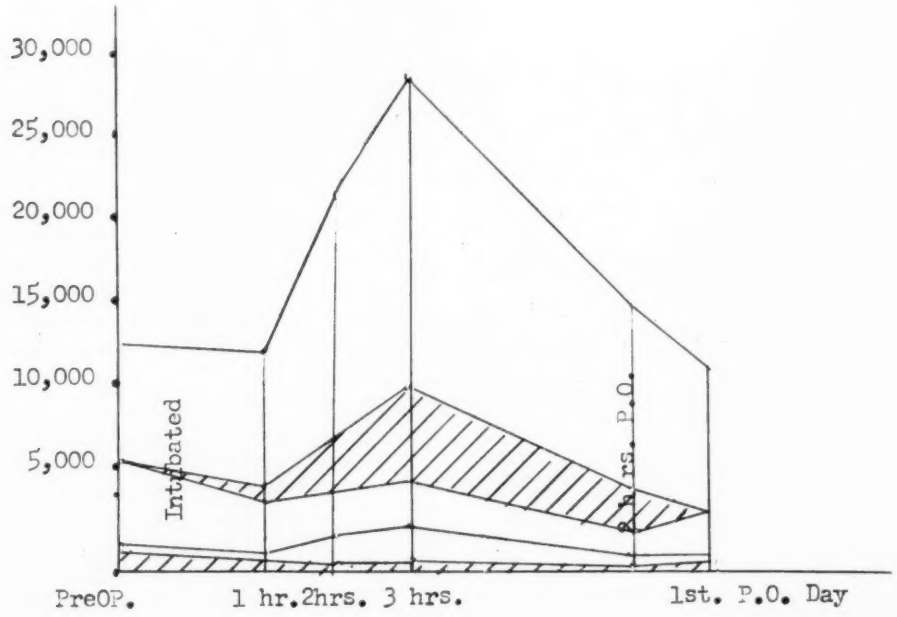
TABLE 2.—*White Cell Response to Thoracoplasty*

		Intubated			Postoperative	
	Preop.	1 Hr.	2 Hr.	3 Hr.	2 Hr.	1 Day
Total count	13,200	13,000	22,250	29,500	16,400	12,650
Leukocytes	6,732	8,060	14,463	18,585	11,316	9,108
Band forms		910	3,115	5,605	2,952	
Lymphocytes	5,280	3,380	2,670	3,835	1,476	2,782
Monocytes	132	520	1,780	1,180	656	380
Eosinophils	1,056	130	222	295		380

ophils and lymphocytes. There is a difference in the magnitude of the responses, the smallest change being due to corticotropin, a larger response to thoracoplasty, and the maximum response to thoracotomy. There is another constant finding in all thoracotomies —this is the marked fall in total count, polymorphonuclear leukocytes, and band forms that occurs between the time the chest is closed and two hours after operation. This marked fall is not seen after corticotropin or thoracoplasty.

Sixth Group.—Two patients had two surgical procedures, each using ether anesthesia and intubation.

One patient (Case 2), a 26-year-old woman, had a spinal fusion on Feb. 26, 1955. Graph 5 shows the white cell response, and Table 3 shows the actual number of each type of cell. On June 30 she had a wedge resection from the posterior subsegment of the left upper lobe (Graph 6; Table 4). This procedure required only 2 hours 18 minutes from the time of intubation, and so the maximum response usually seen during thoracotomy is not seen here. It appears, therefore, that the time element is a significant factor in producing the peak that one sees during thoracotomy. When we compare Graphs 5 and 6, the amount and type of response are seen to be very similar. This was also true in the other patient (Case 3), with a spinal fusion and a nephrectomy. From this it would seem that so long as the reservoir remains



Graph 4

TABLE 3.—*White Cell Response to Spinal Fusion*

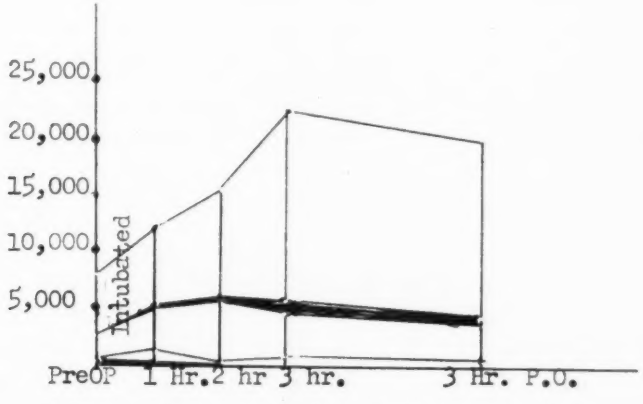
		Intubated			
	Preop.	1 Hr.	2 Hr.	3 Hr.	3 Hr. Postoperative
Total count	8,200	12,200	15,600	22,400	20,050
Leukocytes	5,084	6,954	9,516	16,800	15,839
Band forms		122	312	1,120	602
Lymphocytes	2,870	3,904	5,616	3,808	3,609
Monocytes	164	1,098	156	672	
Eosinophils	82	122			

intact the response to surgical procedure is the same.

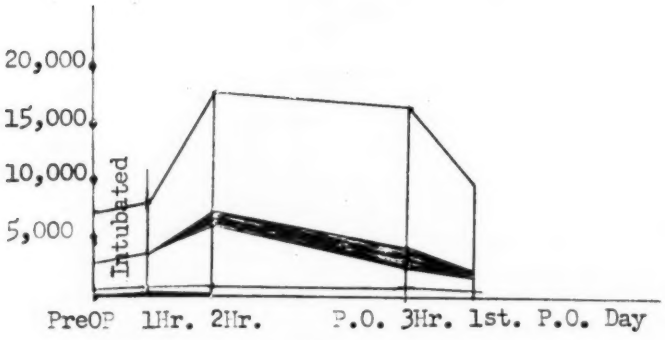
Seventh Group.—To investigate this phenomenon further, white and differential cell counts were done hourly on two patients with gastric resections who had ether anesthesia and were intubated. The response here is similar in type to that seen in thoracotomy, but is less marked in degree. It is greater than that seen with corticotropin but is almost identical with that seen with thoracoplasty after pneumonectomy. This makes one feel that intubation with positive pressure anesthesia is a factor in producing the increase in the white blood cell count and the change in the differential count. In chest surgery, a patient with a white cell count of over 15,000 on the first postoperative day usually shows obvious atelectasis on the routine portable x-ray.

Comment

The mechanism for increasing the white blood cell count in man is not well understood. There are cyclic variations in the count within each twenty-four-hour period. Acute infection is known to produce a rise in the white cell count and a left shift, and this response is greater and more rapid when the lung is involved, as in pneumonia or lung abscess, but it seldom rises above 25,000, whereas the patients with thoracotomy averaged 32,000. The only time a white cell count as high as this has been reported with normal cells is at the time of splenectomy for hypersplenism, when blood is drawn from the splenic vein after injection of epinephrine into the splenic artery—even here the peripheral blood had fewer cells than did the splenic vein.[17] It has been reported that massive hemorrhage may produce a high white cell count, but this could not have been a factor in our cases, for several patients required no transfusion and of those who did require blood, transfusion was not begun until after the maximum cell response had already occur-



Graph 5.—White cell response to spinal fusion (Case 2).



Graph 6.—White cell response to wedge resection (Case 2).

red. The possibility that transfusion itself could increase the white blood cell count is unlikely, because in a heart-lung preparation the lung filters out the granulocytic series,[1] having an almost unlimited capacity. When leukemic blood is cross circulated through a patient with normal lungs, the early forms of the granulocytic series are removed from the circulation during the first passage through the lung,[3,12] but the efficiency in removing early cells of the lymphocytic series is much poorer, so that they do appear in the peripheral circulation.

When epinephrine is given to a patient, there is a prompt rise in the polymorphonuclear leukocytes within minutes, lasting about 30 minutes or less.[14] Epinephrine also produces a fall in the eosinophil count, and in patients before surgery a decreased eosinophil count is frequently found, probably due to the release of epinephrine within the body as a result of apprehension. If epinephrine tests are run in humans and in dogs before and after splenectomy, the polymorphonuclear leukocyte responses in the peripheral blood are the same.[9,10] If epinephrine tests are run with a catheter in the inferior vena cava, the peripheral circulation shows an increase in cells before the splenic vein.[5] If labeled leukocytes are given a patient, most of them stop immediately in the lung.[16] All this indicates that the reservoir for the granulocytic series is the lung and not the spleen, as is commonly stated in textbooks. When epinephrine tests are done in patients with lymphogenous leukemia, the response is small as compared with that in patients with myelogenous leukemia[6]; so the lymphocyte series is not stored, as is the myelogenous series. Among our patients, those whose reservoir was left intact had the same type and magnitude of response to intubation; if the reservoir was decreased by pneumonectomy, the response was delayed and diminished.

When corticotropin is given to patients with intact adrenals, a characteristic response occurs, i. e., an increased white cell count, increased polymorphonuclear leukocytes with a left shift, a fall in the number

Table 4.—*White Cell Response to Segmental Resection*

		Intubated		Postoperative	
	Preop.	1 Hr.	2 Hr.	3 Hr.	1 Day
Total count	7,200	8,200	18,000	16,000	9,850
Leukocytes	4,464	4,264	10,440	12,160	7,979
Band forms			900	1,600	296
Lymphocytes	2,664	3,280	5,580	1,600	1,379
Monocytes	72	410	900	640	197
Eosinophils		246	180		

of lymphocytes, and a decrease of at least 50% in the number of circulating eosinophils.[11] Our five patients who were given corticotropin followed this pattern. However, in the average for the 50 patients with thoracotomy the eosinophil count did not fall quite this much, indicating the possibility that endogenous epinephrine had lowered the count because of stress before surgery was started. In our experience the white cell response to corticotropin is less than that seen in thoracoplasty or gastric resection. The similarity between the white blood cell count the day following corticotropin and the first postoperative day after thoracoplasty or thoracotomy would indicate that the stress of surgery is responsible for this elevated count. If atelectasis is present, then this count has a more marked elevation. In thoracotomy there is a peak in the response that begins two hours after intubation and a prompt fall two and one-half hours after the chest is closed.

How can these effects be explained? First, Bierman[4] showed that with Valsalva's maneuver the white cell count in the pulmonary artery fell and with Müller's maneuver the cell count rose and the granulocytic type of cells were particularly affected. Drinker[8] showed that the flow of lymph from the thoracic duct was decreased by anything that brought the negative pressure within the thorax closer to atmospheric pressure. If the animals were intubated, there was a decrease in lymph flow, and if the chest was opened, the lymph stopped, just as though a spigot were turned. If the lung is a selective filter for the granulocytic series of cells, and if by increasing or decreasing the flow of the lymphatic circulation the cell count in the pulmonary artery can be raised or lowered, then is it not possible that the granulocytes have their own circulatory system from the lung into the lymphatics, then to the subclavian vein, and back to the lung again? When this circulation is stopped temporarily, the lung can no longer filter out these cells, and so they appear in the peripheral circulation. When this circulatory system is again established, the lung removes these cells from the peripheral circulation very quickly. Recalling the peak effect seen in thoracotomy, it would seem that this circulation takes about two and one-half hours. This would explain why, in gastric resection, the peak effect does not occur because the lymphatic circulation is decreased but not stopped. It might also explain why patients in labor, and those with excessive nausea and vomiting or convulsions have an increased white cell count.

The appearance of many band forms during thoracotomy indicates that almost one-fifth of the granulocytes are early forms; so it is probable that the granulocytes are released from the bone marrow as band forms and matured in the lung.

Conclusions

1. Pulmonary artery blood at thoracotomy has a high white cell count, three times the preoperative level, appearing predominantly in the granulocytic series, with a marked left shift.

2. Peripheral blood, arterial or venous, has this same elevated count with the marked left shift three hours after intubation and two to three hours after the chest is opened. The type of pulmonary resection, sex, or side of the chest opened did not vary the response.

3. The count falls 50% within two hours after the chest is closed, but the left shift persists. Further fall occurs during the next 24 hours unless there is postoperative atelectasis.

4. Lymphocytes show a small rise at the time of maximum response, then fall quite markedly, remaining low on the first postoperative day.

5. Monocytes increase and remain increased during thoracotomy and the first postoperative day.

6. Eosinophils disappear in most patients with thoracotomy.

7. This great response in the granulocytic series represents a release of over 60 gm. of cells, or 120,000,000,000 cells.

8. There are at least two factors responsible for these changes.

(*a*) One is the response to corticotropin released by stress (but this response is less than half the total).

(*b*) Another is probably the loss of the ability of the lung to act as a reservoir for the granulocytic series of cells, thus releasing them into the peripheral circulation.

9. New cells are not released from the bone marrow; so this is not a factor in the marked rise in cell count, increase in the granulocytic series, and marked left shift.

10. A granulocytic response occurs with any surgical procedure if the patient is intubated for two and one-half to three hours, even though the chest is not opened. Thoracotomy increases the response.

11. The response of a patient is similar in two surgical procedures so long as the lung volume has not been decreased by the first operation.

14 W. Orchard.

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Adrenalectomy for Severe Hypertension

A Follow-Up Report

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In 1954 a report was published describing bilateral adrenalectomy for patients with severe hypertension.[1,2] These operations were performed in what now can be termed the "pre-drug era," when the effectiveness of hypotensive drugs was not established. Consequently, the follow-up studies are made on a group of nine patients whose postoperative period is now four to six and one-half years. Obviously, when drugs became available, adrenalectomy was abandoned because one must induce hypoadrenalism to accomplish surgical relief by adrenalectomy. The hypoadrenalism is a major illness in itself, and the operation must not be used except for patients with severe hypertension whose tension is uncontrollable by other means. A few patients were subjected to bilateral adrenalectomy in the "post-drug era" when the drugs failed to invoke a desirable lowering of the blood pressure, but the surgical results were not good because most of the patients were too ill then to tolerate the operation.

Case selection of the 35 patients, with one exception, indicates severity, and nearly all were too ill for thoracolumbar sympathectomy. Competent medical observers confirmed the severity in nearly every instance and utilized the usual conservative medical judgment and reluctance to attempt a surgical procedure of questionable promise. The result therefore as to selection meant that we received only the very sick patient for consideration, and, according to the medical advisers, the selected patients were otherwise doomed to certain death within the next few months; only one patient was believed to have lingered longer than one year.

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Follow-Up Report

Technique.—A two-stage transabdominal removal was accomplished. The left adrenal was removed first, a small bit of the left adrenal being left at the lower pole of that gland. This remnant was the size of an average blackberry. Several weeks later adrenalectomy was done on the right side. For the past two years we have employed the one-stage procedure, removing both adrenals, with no added mortality or morbidity, and we plan to continue the one-stage operation except perhaps in a few extremely ill patients.

Mortality.—Operation was performed in 35 patients. There were 22 survivors of the 28 patients operated on in the "pre-drug" group. In the entire group, there were 27 survivors and 8 deaths. Six patients died after the first stage; one patient, after the second stage, and one patient, after bilateral adrenalectomy in one stage. The operative mortality was much higher during our early experience, mainly because we were not certain how ill the patient could be and still survive the operation. We found, however, that the state of renal function was the real measure of the patient's ability to tolerate the operation. Multiple cerebral vascular accidents, controllable cardiac decompensation, and extensive arteriosclerosis were not necessarily contraindications.

Longevity.—The accompanying Table denotes length of time since operation. It will be noted that many of these patients have

Adrenalectomy for Hypertension: Present-Day Survivors

	Case No.	Average Blood Pressure	Postoperative Follow-Up, Yr
Pre-drug era	1	200/100	6-6/12
	2	160/100	6-5/12
	3	130/ 95	6-4/12
	4	130/ 95	6-3/12
	5	170/110	6-2/12
	6	150/ 90	6-1/12
	7	210/130	5-11/12
	8	175/110	5-5/12
	9	110/ 60	4-2/12
Post-drug era	10	170/115	1-6/12

survived more than six years and, with one exception, are normotensive, or nearly normotensive. Experience with adrenalectomized patients, as in the drug-treated patients, indicates that certain patients live much happier if they remain slightly hypertensive. This level is, of course, regulated by the amount of cortisone and desoxycorticosterone acetate administered in the substitutive therapy. The ability to achieve a satisfactory lowering of pressure by adrenalectomy in this investigation proves to be in the neighborhood of 70%. Roughly, one-third of the patients failed to receive satisfactory reduction, but a few have received additional lowering of pressure by the added use of hypotensive drugs. We have learned also that the study of blood pressures in these patients can be confusing. For instance, if the patient has been walking fast, running, or doing other physical exertion, a reading of the pressure at that time will often be higher (i. e., 190/110), but if the patient is permitted to rest about one-half hour, the reading will then be lower (i. e., 160/110).

Substitutive Therapy.—Difference in response to substitutive therapy poses a difficult problem for solution. We feel that the small remnant left in the "pre-drug-era" patients had been of no consequence in the prevention of serious and fatal hypoadrenalism. Obviously, the postoperative substitutive therapy will induce functional atrophy of the remnant. In spite of this, one patient takes no cortisone; one patient takes 10 mg. of cortisone daily; one patient, 20 mg.; two patients, 30 mg.; one patient, 50 mg., and an occasional patient takes as high as 60 to 75 mg. of cortisone daily. Space will not permit a description of our early difficulties with postoperative management; in brief, we have learned how to create a proper balance, and, as postoperative time increases, the substitution problem becomes easier, for the patient, even though not highly intelligent, soon learns to take a larger dose of cortisone, a higher intake of salt, or to consult his physician when certain of the prodromal symptoms arise. The statement "that control for the adrenalectomized hypertensive patient is more difficult than for the nonhypertensive adrenalectomized patient" is probably correct. For instance, anorexia, weakness, nausea, and vomiting are often present many days before the blood pressure falls to a hypotensive level; if the dose of cortisone is not increased or salt administered during this early phase of the deficiency, uncontrollable hypoadrenalism can cause the death of the patient. Six patients died of hypoadrenalism—four in our hospital and two elsewhere. Our four patients died in the early days of our experience, when we did not well understand the substitutive therapy. All of the nine survivors know when to increase the cortisone dosage in excessively hot weather, stress of illness or emotion, or a minor febrile episode, such as the common cold, laryngitis, or bronchitis. A recent instance of mild hypoadrenalism followed influenza complicated by pneumonia. The patient increased his cortisone dosage, but not enough to meet the demands of the serious febrile illness. Control was easily obtained by proper treatment of pneumonia with an increase in the cortisone intake. One can say that the postadrenalectomy period was a dangerous condition seven years ago, but, today, with a better understanding of the substitutive therapy, it is now regarded as relatively safe. Furthermore, these patients have not shown many ill effects from the long cortisone therapy—not as many as we

anticipated. A few patients developed gastrointestinal bleeding, undoubtedly due to cortisone-induced gastrointestinal ulceration, but only one required operation. A successful gastric resection was performed six years after the miraculous salvage of a paralyzed, blind, and twitching patient with malignant hypertension. The operation was well tolerated and the incision healed per primam. There was moderate infection in the drainage site.

Progress of Cardiovascular Disease.—Clearly, hypertensive cardiovascular manifestations produced deaths in the one-third (seven) of the patients who received no benefit from the operation. The living patient who still remains hypertensive, although at a much lower level than preoperatively, demonstrates this point with myocardial insufficiency.

Two patients died of coronary thrombosis; two of cerebral vascular accidents, and two of kidney failure.

It would be pointless to describe in great detail the cause of death in each patient, because many of them died of causes unrelated to the hypertensive disease. In general, one can state that a few of them died of cardiovascular illness, but many months, or even years, later than if the hypertension had not been lowered by adrenalectomy. The cause of death of those patients whose hypertension was not improved after the operation was invariably some phase of the caridovascular-renal complex.

Follow-Up Case Facts

Case 1.—Six and one-half years postoperative; blood pressure 200/100; requires 70 mg. of cortisone daily; has had several serious gastrointestinal hemorrhages due to "cortisone ulcers." Successful gastric resection was performed in August, 1957. This patient was totally blind and paralyzed preoperatively, shows slight residuals of paralysis, walks with a cane; his eyesight permits reading of large print; can dress and feed himself; does not work but is very happy and very grateful for the benefit from operation.

Case 2.—Six years five months postoperative; blood pressure 160/100; requires 20 mg. of cortisone daily; drinks heavily; is often jailed for alcoholism; recently underwent successful surgical bypass homograft of the carotid artery for block due to arteriosclerosis and slight stroke. He has not worked; for the past eight months he has not drunk; he appears healthy.

Case 3.—Six years four months postoperative; blood pressure 130/95; requires 15 mg. of cortisone daily; is in apparent good health; stopped preoperative work as a farmer; now works daily conducting business of a small grocery store.

Case 4.—Six years three months postoperative; blood pressure 130/95; requires 30 mg. of cortisone daily; appears healthy; has marked pigmentation due to hypoadrenalism; works daily at a parking garage; is extremely happy; is the only hypertensive member in his immediate family who has not died in a short time of the disease.

Case 5.—Six years two months postoperative; blood pressure 170/110; requires 10 mg. of cortisone daily; is healthy-looking; pulse regular (pulsus alternans preoperatively); works half-day at insurance work.

Case 6.—Six years one month postoperative; blood pressure 150/90; requires 15 mg. of cortisone daily; works intermittently; appears healthy; no cardiovascular manifestations.

Case 7.—Five years 11 months postoperative; blood pressure 210/130; takes no cortisone; does not work; cardiac failure. Condition improved as compared with his preoperative hypertensive state, but case is considered a failure and patient will probably die of the disease. He does not work.

Case 8.—Five years five months postoperative; blood pressure 175/110; requires 30 mg. of cortisone daily; is obese and jovial; did not work before operation but does "odd jobs"; he is very pleased with result.

Case 9.—Four years two months postoperative; blood pressure 110/60; requires 50 mg. of cortisone daily; does light work; looks healthy.

Of these nine patients, there is one with an arteriosclerotic block in the carotid artery and one with cardiac insufficiency who is regarded as an operative failure. The other seven patients lost their preoperative hypertension and now show no increase in any phase of their hypertensive disease. Marked improvement in the eyegrounds, in the number of cerebrovascular accidents, and in cardiac activity has been usual, although no improvement in kidney function is manifested.

One cannot help but be impressed with the favorable course of these survivors and with the longevity which has been achieved. Factually, the results are far better than

we anticipated. One wonders whether a like number of survivors in relatively good physical condition will be had by medical therapy in patients as sick as these. Obviously, adrenalectomy must not be employed unless the patient fails to achieve lowering of pressure with drug therapy. Our "post-drug" experience indicates that it would be preferable if failure by medical treatment could be established promptly and adrenalectomy employed before the patient's general condition was so poor that operation could then be done only with great danger.

Summary

The fate of 22 patients who survived bilateral adrenalectomy is reported.

Longevity, present average blood pressure levels, amount of cortisone, and brief statements of present health, ability to work, and presence or absence of hypertensive organic manifestations are noted.

Undoubtedly, better results have been achieved than was expected.

Long administration of cortisone in not too large doses is fraught with danger, but not to the extent that it should contraindicate bilateral adrenalectomy if that is needed.

There will be no need for adrenalectomy in hypertension when drug therapy will accomplish reduction of pressure and longevity.

This study indicates that certain patients, when medical failure exists, may well benefit from adrenalectomy if the operation is performed before the patient's condition clearly contraindicates this type of surgery.

VA Medical Teaching Group, Kennedy Hospital (15).

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Cation Exchange Resins in the Treatment of Hyperkaliemia

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The treatment of patients suffering from acute renal insufficiency has improved remarkably in the past 10 years. Renal insufficiency secondary to obstructive uropathy and fluid and electrolyte imbalances are more regularly detected and better treated. In addition, nutritional and fluid management is fairly well delineated for the acute renal insufficiency related to primary renal disease, and the more especially that associated with acute tubular necrosis.

Although the artificial kidney has been used extensively in treating uremia, it has certain disadvantages: A trained team and relatively expensive equipment are needed; a large quantity of blood may be necessary for priming the apparatus, and operative procedures are necessary to effect connections between the dialyzer and the patient's blood vessels. Furthermore, rapid changes in the plasma electrolyte pattern are generally effected in order that vascular perfusion of the patient is not prolonged unduly. This forces the patient, who is frequently dangerously ill, to adjust to large variations in his body fluid constituents. This effect is most obvious with reference to the potassium ion. The following case exemplifies this.

A 47-year-old white farmer was bitten by a black widow spider and for four days thereafter passed no urine (Fig. 1). At that time he was transferred to Barnes Hospital and already showed signs of severe uremia with some degree of hyperkaliemia. Dialysis was performed shortly after his admission, and all the signs and symptoms of uremia were dissipated. Subsequently, the flow of urine was disappointingly meager, and additional dialyses were required every three to five days. Following each dialysis there was a complete reversion of the electrocardiographic signs to normal and recovery of a lucid mental state. The accompanying graph (Fig. 1) illustrates the great swings which were produced in both the serum potassium and the nonprotein nitrogen level. At no time during the 27 days he lived after his injury did the urinary output exceed 100 ml. per day. He

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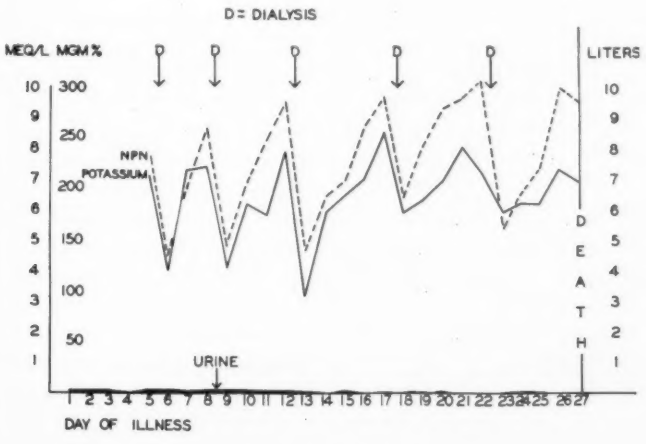

Fig. 1.—Graph illustrating variation in serum metabolic levels induced by extracorporeal dialysis.

finally succumbed to an overwhelming infection, originating in the incisions made to permit placement of the dialysis catheters. Variations in serum metabolite levels, such as those illustrated by this case, might be prevented should means be found to effect their steady removal by some extrarenal route during a period of renal failure.

In 1950, Elkinton [1] made the suggestion that cation exchange resins might be effective in the control of hyperkaliemia. While the initial reports concerning their clinical effectiveness were encouraging, relatively little has been done with them lately. This lack of interest in the exchange resins may be related to two causes. First, fecal impaction has been noted frequently. The resins used originally were prepared as fine powders in order to make oral ingestion easier. Many uremic patients, however, because of nausea and intestinal distention, are unable to eat, and when the powdered resins suspended in water are administered as an enema, they form concretions. This practically abolishes the effectiveness of the resins and produces fecal impaction. Second, in comparison with extracorporeal dialysis, the rate of potassium removal by the exchange resins is relatively slow. Once hyperkaliemia is evident on a clinical basis by virtue of changes in signs and symptoms, alterations in electrocardiogram, and elevation of the serum potassium, there is frequently a need for rapid action. Under these circumstances the principal beneficial effect of the exchange resins, a slow, smooth removal of potassium, is of little value. While the ion exchange may be enhanced by the administration of large quantities of resin in frequent enemata, this treatment is cumbersome and does not compare favorably with a well-conducted dialysis.

However, the exchange resins can be used effectively in the treatment of uremia, and in some instances their use has obviated the need for dialysis. The following paragraph is a summary of the more pertinent data concerning the exchange resins.[2]

The exchange resins adaptable to the treatment of uremic hyperkaliemia have two components: the resin base and the attached groups which bind the exchangeable ions. In general, the resin base consists of long-chain polymers, which are cross linked by shorter molecules, forming a lattice structure so constituted as to be inert and completely insoluble. The surface area of the resin may be expanded by decreasing particle size by grinding or limiting polymerization. Increasing the number of cross linkages makes a lattice structure which is tighter and limits the degree of swelling of the resin particles when hydration is effected. These alterations affect the exchange capacity of the resin by expediting or retarding the passage of exchangeable ions through the lattice. The active groups of the cation exchangers are bound to the resin base at multiple sites through the latticework. They consist of either strongly ionized (sulfonic) or weakly ionized (carboxylic) acids. The extent of dissociation of the acidic groups determines the efficiency of the ion exchange at various pH's. In general, the strong electrolyte (sulfonic) resins are active throughout the entire pH range, while the weakly dissociated (carboxylic) resins exchange less rapidly at low pH's. The hydrogen ion of the acid group is the ion which is displaced in the exchange process, and is designated as the counter ion. The effect of an exchange resin when placed in a solution of one or more ions is directly proportioned to the concentration of the individual ions in the solution, in comparison with their individual concentrations within the resin. It is directly proportional to the individual ionic radii. In a solution, therefore, of two cations of nearly equal ionic radii and identical valances, the rate of exchange within a resin charged with a foreign ion will be very nearly the same, but there will be relatively more total exchange for the ion present in the highest concentration in the solution. If, however, the resin is charged with one of the ions in question, exchange will be confined almost completely to the other ion. A short-radius ion will exchange

more rapidly than one with a long radius, and multivalent ions have higher exchange potential than univalent ones. Most of the exchange resins now being manufactured have exchange capacities of 3 to 5 mEq. of cation per gram of dry resin.

The type of ion which is used to charge the resin has, in our experience, not been of clinical significance. At the current rate of ion-exchange efficiency, we have been unable to detect any obvious differences between the use of sodium-charged and ammonium-charged resins. In no case have we observed significant alteration in extracellular fluid volume or osmolar concentration caused by the administration of sodium ion through exchange for potassium ion.

The exchange resins are nontoxic. In the course of treating over 40 patients with cation exchange resins, no adverse effects of the resins were encountered. The only difficulties noted during their use have been technical in nature. Fecal impaction from concretion of the resin particles has not been seen since we have suspended finely ground resins in hypertonic (10%) dextrose solution before introducing them into the colon.

Initially use of the resins was limited to the treatment of those patients demonstrating the signs of illness attributable to observed hyperkaliemia. Under these circumstances it became apparent that, although some beneficial effect was regularly observed, resin treatment was not ideal. Nonetheless, a few patients with high serum potassium levels were successfully treated with the resins, and this experience encouraged us to study the resins further. Examples of effective use of the resins in such patients follow.

A 37-year-old woman became oliguric after the administration of O-Rh-positive blood during a Cesarian section (Fig. 2). She had had a previous Cesarian section 12 years before this one and had been transfused. The patient's blood was O-Rh negative, and that of the donor was incompatible O-Rh positive. Despite the administration of large amounts of dextrose, severe hyperkaliemia was evident on the fourth day. When the serum potassium attained a concentration of 8 mEq. per liter, the electrocardiogram showed high-peaked T-waves and spreading of the QRS complex. Exchange resins suspended in 10% dextrose solution were administered by enema in the amounts indicated in Figure 2. Despite a rising nonprotein nitrogen and an inadequate urinary output, the serum potassium level was reduced to normal, and complete reversal of electrocardiographic changes took place. Thereafter hyperkaliemia was not a problem.

In the second case, a 67-year-old white woman had had chronic renal disease for several years. She became severely oliguric upon being stricken with an acute urinary tract infection. When she was admitted to Barnes Hospital, her serum potassium level was 8 mEq. per liter, and the expected ab-

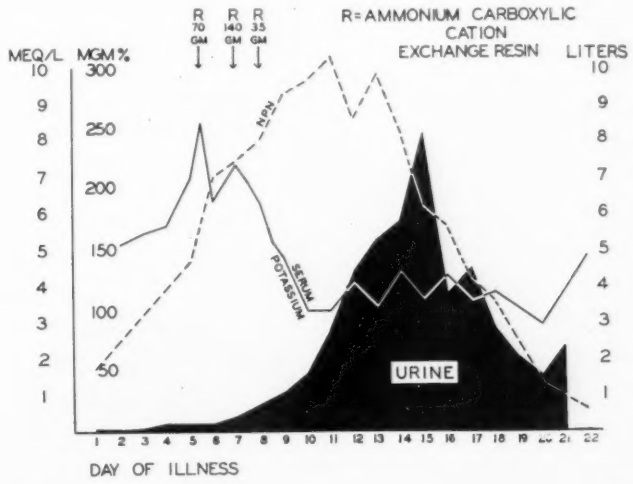

Fig. 2.—Treatment of severe hyperkaliemia with cation exchange resin. The serum potassium level fell to normal prior to onset of diuresis.

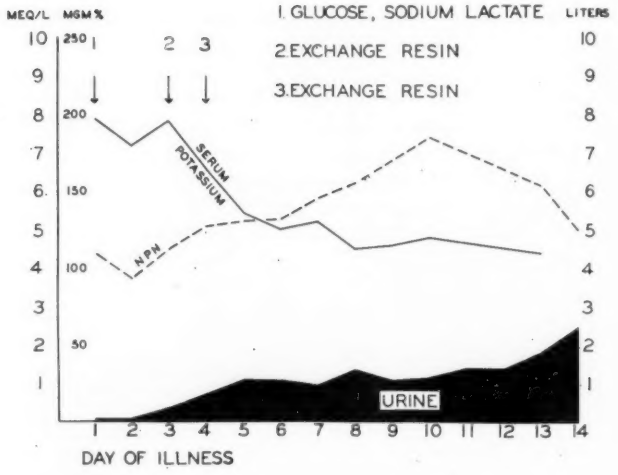

Fig. 3.—Treatment of severe hyperkaliemia with cation exchange resin in a patient with an acute exacerbation of chronic renal failure.

normalities of the electrocardiogram were found. The administration of 50% dextrose solution and insulin intravenously effected slight reduction of the serum potassium level, from 8 to 7.5 mEq. per liter, without modification of the electrocardiogram. The following day, with a serum potassium level again at 8 mEq. per liter, exchange resins were given rectally, as indicated in Figure 3. A total of 150 gm. of resin was given during three days. With the use of the resin, the potassium level fell to normal, and the electrocardiographic changes disappeared.

As the potassium level in the serum fell while the nonprotein nitrogen level was still rising, and as the urinary output of potassium was inadequate to effect reduction in serum potassium, we feel that the beneficial effects in these two cases must be ascribed to the use of the cation exchange resins.

As a consequence of these experiences, we institute exchange resin treatment when the serum potassium rises above 5 mEq. per liter or when a steady rise is evident, even at lower levels. When these indications are followed, small doses of resin are used and can be given over many days. Two examples follow.

A 17-year-old white girl had a puerperal hemorrhage and received 4 units of blood, one of which was incompatible. Oliguria followed this. Significant hyperkaliemia was apparent on the sixth

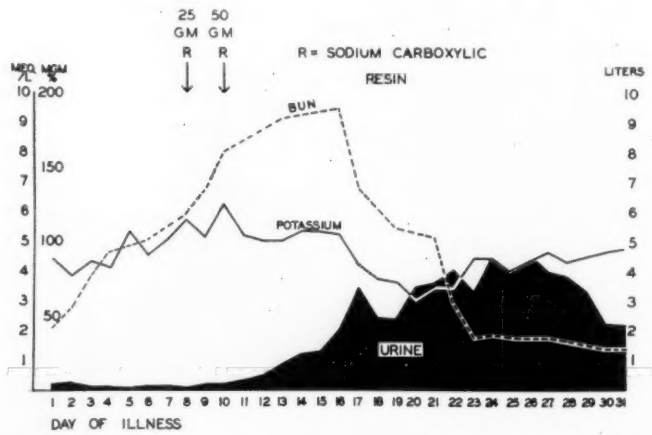

Fig. 4.—Relatively early treatment of hyperkaliemia with cation exchange resin.

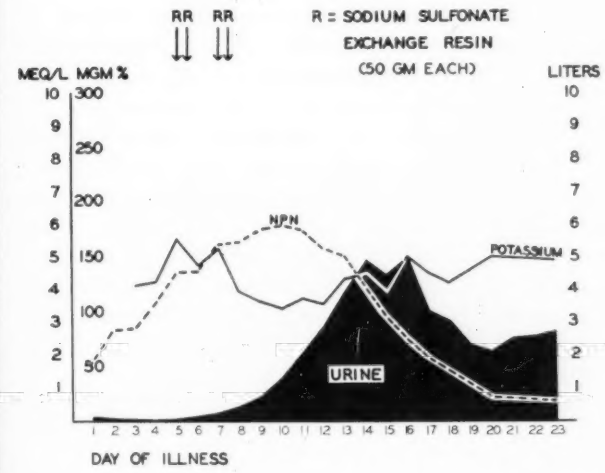

Fig. 5.—Early treatment of hyperkaliemia with cation exchange resin.

day, and exchange resins were given (in 10% dextrose) by enema, as indicated in Figure 4. Coincident with the use of the resins, hyperkaliemia disappeared and did not recur.

In the next case, a 26-year-old white married woman, following the delivery of a normal infant, received a transfusion of whole blood. After the administration of 200 ml., the patient developed chills and fever, and transfusion was stopped. The blood was proved to be incompatible. Oliguria ensued. Although the patient outwardly seemed to remain quite well, the serum potassium level began to rise (Fig. 5) and was associated with specific electrocardiographic abnormalities. Exchange resin therapy was effective, and hyperkaliemia was not again a problem.

Technique

The effectiveness of cation exchange resin treatment of hyperkaliemia is directly proportional to the skill and persistence of the person who administers the enema. When repeated instillations must be made, topical anesthesia of the anal and perianal skin is of some value. The enemata are more easily retained when small amounts of warm solutions are directed slowly into the high sigmoid colon. The patient should be placed on his right side with the hips slightly raised. The resins should be stored in distilled water so as to provide maximum expansion through hydration of the resin particles. Mixtures of the resin with dextrose solution (10%) should be fresh to avoid oxidation and degradation of the resin structures. A minimum of the resin vehicle should be used to avoid expansion of the total body fluids. While our initial work dealt almost exclusively with the use of finely powdered, weak electrolyte (carboxylic) resins, equally good results have followed the use of large-particle, strong electrolyte (sulfonic) resins. The tendency toward impaction is diminished because of the large size of the particles, and these resins may be suspended either in tap water or in dextrose solution (10%). They, at times, cause mechanical injury of the rectal and anal mucosa. We are currently investigating the possible advantages of utilizing strong electrolyte resins in finely powdered form suspended in slightly hypertonic solutions. Because no difficulty with impaction has been observed, every effort is made to induce the patient to retain the enema indefinitely, permitting maximum effect of the resin. In practice, a cleansing enema is administered once every 24 hours, or oftener if the volume of resin which has been necessary to control the hyperkaliemia becomes too great for efficient utilization.

There is wide individual variation in the rate of extracellular fluid potassium elevation from patient to patient during acute renal failure. This is seen as a result of the

previous state of potassium metabolism, unusual losses (extrarenal) of potassium, and unusual sources of potassium gained through breakdown of transfused blood, destruction of tissue, or unknown causes. It is therefore next to impossible to predict the exact rate of potassium accumulation or the time of onset of hyperkaliemia; however, guided by careful clinical observation, it may be possible to begin small doses of resin (20 to 30 gm. daily) almost immediately upon discovery of renal shutdown, thus removing the rather small daily accumulation of potassium in a prophylactic fashion. If, in the future, similar methods can be found for reducing the effect of other toxic factors in the uremic patient, the necessity for extracorporeal dialysis may be still further decreased. At present, in any event, the use of cation exchange resins sufficiently early in the clinical course of the acutely anuric or oliguric patient usually reduces the necessity for dialysis in the treatment of hyperkaliemia or prolongs the interval between dialyses.

Summary

Hyperkaliemia remains a prime indication for extracorporeal dialysis in the treatment of acute renal failure. Extracorporeal dialysis, while effective, is a somewhat complicated procedure.

Cation exchange resin therapy, when administered early in the course of acute renal failure, is effective in the prevention and treatment of hyperkaliemia and is without risk.

Cation exchange resin therapy, properly employed, may eliminate the necessity for dialysis or prolong the interval between necessary dialyses in the treatment of acute renal failure.

The Smith, Kline & French Laboratories, Eli Lilly & Company, and Winthrop Laboratories supplied the resins used in this study.

Dept. of Surgery, Barnes Hospital, 600 S. Kingshighway (10).

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The Tissue Committee and the Appendicitis Problem

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In accordance with a directive issued by the Joint Commission on Accreditation of Hospitals, we at the Newark Beth Israel Hospital organized a Tissue Committee, which began to function in 1955. The physicians appointed were thoroughly briefed as to the purpose of this committee, and worked in close cooperation with the various departments of the hospital to establish a list of recommended and acceptable indications for surgery.[1] The justification for surgery was based upon the history, physical examination, and operative findings, but the final opinion as to the pathological changes in the organ removed was based not on the surgeon's description but entirely upon the pathologist's report.

Experience throughout the country [2-4] has shown that when the Tissue Committee questions the justification of the surgery performed, the offending procedure is most frequently a gynecologic operation or an appendectomy. This report is concerned only with the question of appendicitis. The rules formulated by the Committee approved as justifiable appendectomy only those cases in which the pathologist reported acute inflammatory changes in any of its stages, and, in addition, those cases in which he demonstrated obstruction to the lumen by worms or fecoliths, even though no acute inflammatory changes were present. When the surgeon's postoperative diagnosis was mesenteric adenitis, or the pathologist's diagnosis was lymphoid hyperplasia of the appendix, or chronic appendicitis, the Committee felt it could not approve the surgical procedure, even though the history was suggestive of appendicitis. No one questioned the integrity of a physician who operated for an acute appendicitis but removed an appendix in which the pathologist could find no acute inflammatory disease or obstruction. However, medical teaching and opinion change with time, and what was once considered good medical practice may now, in the light of present-day knowledge, not be considered justifiable surgery.

Twenty-five to thirty years ago acute appendicitis was considered a very serious disease that carried a mortality from 5% to 20% in the gangrenous, perforated type in older persons. At that time the medical profession embarked upon an intensive educational campaign urging the public not to neglect a stomach ache and not to take a cathartic for abdominal cramps, but, rather, to seek medical advice early. In 1939 Bowers [5] was able to report that in Philadelphia, because of such a campaign, the over-all death rate for appendicitis had been reduced from 5.97% in 1929, to 2.44% in 4186 cases. In addition, the medical profession was more insistent upon operating earlier on those patients who presented symptoms suggestive of appendicitis. In the days before the advent of the sulfonamide drugs and the antibiotics, the fear of peritonitis was so great that appendectomy may have been performed even on slight suspicion, with the result that many of the appendices removed showed no inflammation upon microscopic examination.

In a survey made at our hospital of the operations performed in a five-year period (1935 through 1939) for a diagnosis of acute appendicitis, only 45% of the appendices removed showed evidence of acute inflammation upon microscopic examination. However, it was stated at that time that these figures did not discredit the physician;

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Attending surgeon, Beth Israel Hospital; Chairman of the Tissue Committee.

TABLE 1.—*Emergency Operations in Cases with Preoperative Diagnosis of Acute Appendicitis*

Pathological Diagnosis	1952	1953	1954	1955	1956
Acute	243	239	224	228	221
Obstructive	37	19	27	28	11
Chronic and lymphoid hyperplasia	181	192	168	167	71
Total	461	450	419	423	303

in fact, they were offered as proof that the physician was keenly aware of the early signs and symptoms of appendicitis. It was believed that it probably was better to remove one appendix unnecessarily than to risk one patient's life by waiting too long.

Today, such reasoning is not considered to be medicine at its best. The consensus is that in a well-run hospital the disagreement between the clinician's diagnosis and the pathologist's report should, in the cases of appendicitis, not exceed 20%. The profession still believes in early operation, but only after the patient has been carefully observed for a period long enough to permit the physician to make a more accurate diagnosis. It is recognized that a delay of a few hours will not harm the patient if he is put to bed, deprived of oral feeding, and given no medication to mask symptoms.

Though our Tissue Committee began to function in 1955, the full effects of its efforts were not realized until 1956. Table 1 shows all the emergency operations performed at the Newark Beth Israel Hospital with a preoperative diagnosis of acute appendicitis during the five-year period of 1952 to 1956. It will be noted that for the first four years the total number of cases in each year did not vary greatly (461 to 419). In 1956, however, when the recommendations of the Tissue Committee were more generally observed, there was a decrease of about 35% in the number of operations performed. If one will observe the three pathological classifications in the Table, it will be noted that the number of cases of pathologically acute appendicitis remained about the same in all five years, whereas in the cases of so-called chronic appendicitis there was a drop from the four-year average of 177 cases to 71—a decrease of about 60%.

It will be noted in Table 2 that in the cases of pathologically acute appendicitis male outnumber female patients in all five years. In those cases in which operation was performed for acute appendicitis, but not substantiated by the pathologist's report, women outnumber men 3 to 2 in the first four years of this survey. (This relationship between male and female in this condition was found to be the same in our 1940 survey.) For the first four years of the present survey, the average number of women operated upon for acute appendicitis, but in whom this condition was not found, was 108. In 1956, however, it will be noted that the number of women in this category who were operated upon was only 28, a reduction of 80%. Since most of these cases occurred in women who were in the childbearing period, their complaints may have been due to the changes occurring in the menstrual cycle rather than to appendicitis. This suggests that with a thorough history and a more careful evaluation of symptoms, mittelschmerz apparently can be differentiated from appendicitis and operation avoided.

At the start of this program some of the physicians were worried about the Committee's recommendations, fearing that the delay in operating might result in a greater number of ruptured appendices, with a possible increase in the mortality rate. These were the physicians who believed it better to err on the side of safety by removing a possibly normal appendix than risk one patient's life

TABLE 2.—*Sex Distribution in Cases of Acute Appendicitis*

Pathological Diagnosis	Year	Male	Female
Acute and obstructive	1952-1955 (Average)	154	107
	1956	138	94
Chronic and lymphoid hyperplasia	1952-1955 (Average)	69	108
	1956	43	28

by waiting too long. Apparently, these fears were not well founded, for it has been our experience that with proper care the number of unnecessary operations can be reduced without increasing morbidity or mortality.

Table 3 shows the mortality rate for the past five years. It will be noted that in the 1277 cases of the acute inflammatory or obstructive type there were 3 deaths—a mortality rate of 0.23%. In the 779 cases in which operation was done for acute appendicitis but in which the pathological diagnosis was chronic appendicitis or lymphoid hyperplasia, there were also 3 deaths—a mortality rate of 0.38%. In this latter group, one death was due to a cardiac arrest on the operating table in a 5-year-old child. Another death occurred in a young woman who suddenly went into shock when the peritoneum was opened. The third fatality occurred in a young man who was a known hemophiliac and who bled to death after the operation. A study of Table 3 permits the assumption, apparently, that it is not safer to remove one appendix unnecessarily than to wait for more definite signs of acute inflammation of the appendix.

Table 4 shows that in the survey of 1940 in only 45% of the cases operated upon for acute appendicitis did the diagnosis prove to be such by microscopic examination. In the years 1952 to 1955 the diagnosis of acute appendicitis was corroborated by the pathologist in 59.5%. However, that percentage of correct diagnoses was not high enough to fulfill the requirements of the Accreditation Committee, and the Tissue Committee's program was set up to correct this, if possible. As stated before, our Committee was organized in 1955, but the effects of its recommendations were not noticeable until 1956. In that year our error of diagnosis of acute appendicitis was reduced to 23.3%. In 1957 the mistaken diagnoses were still further reduced to 21%.

TABLE 3.—*Mortality Rate for Appendicitis*

Pathological Diagnosis	Cases	Deaths	Per Cent of Deaths
Acute and obstructive	1277	3	0.23
Chronic and lymphoid hyperplasia	779	3	0.38

TABLE 4.—*Microscopic Diagnosis in Operations for Acute Appendicitis*

	1936-1940	1952-1955	1956	1957
Correct diagnoses	45%	59.5%	76.7%	79%
Incorrect diagnoses	55%	40.5%	23.3%	21%

Summary and Conclusions

It should again be stressed that acute appendicitis is definitely a surgical disease which requires early surgery. However, every bellyache is not appendicitis, and it is the responsibility of the surgeon to be certain of his diagnosis before embarking on surgery. Within two years of the organization of our Tissue Committee, the proportion of correct diagnoses was raised from 59.5% to 76.7%. One must be especially alert when treating women in the childbearing age, for our experience has shown that disturbances occurring in the menstrual cycle may be confused with appendicitis. At the Newark Beth Israel Hospital there has been an almost 80% decrease in the number of women unnecessarily operated upon for mistaken diagnosis of acute appendicitis, possibly as a result of the functioning of the Tissue Committee. At the same time there has been no increase in the morbidity or mortality rate.

This survey confirms two facts.

1. With proper care acute appendicitis can be quite accurately diagnosed and appendectomy performed with an extremely low mortality (0.23%).

2. The recommendations of the Joint Commission on Accreditation of Hospitals and our Tissue Committee are apparently sound and safe.

89 Lincoln Park.

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Clinical Application of a New Flexible Knitted Dacron Arterial Substitute*

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The direct surgical treatment of various forms of aortic and arterial disease often requires a vascular replacement. Homografts were first employed successfully for this purpose and both technically and functionally have provided gratifying results. Their major disadvantage, however, lies in the inconvenience associated with their procurement and preparation, and the fact that they are not available in sufficient quantities to meet the increasing demands for their use. For these reasons attention has been directed toward development of a satisfactory arterial substitute for homografts which would be free of these disadvantages. In cooperation with Prof. Thomas Edman, of the Philadelphia Textile Institute, a new flexible knitted Dacron tube has been devised which on the basis of experimental and clinical studies has been found to meet this objective. Among its desirable characteristics are the following: First, it may be repeatedly sterilized by autoclaving in the usual manner without harm to or weakening of the fabric. Second, owing to its knitted construction, it is nonfraying and may be cut with the scissors or scalpel at any angle, or holes may be cut in its side for anastomosis of branches. Third, it is flexible and elastic, thus facilitating its anatomical and technical application. Fourth, it may be clamped with arterial clamps without harm to the fabric. Fifth, it is available in tubes of various sizes and shapes, including secondary branches for ready adaptability to all segments of the major arterial system. This exhibit demonstrates the clinical application of this arterial substitute based upon our experience in 737 cases.

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From the Cora and Webb Mading Department of Surgery, Baylor University College of Medicine.

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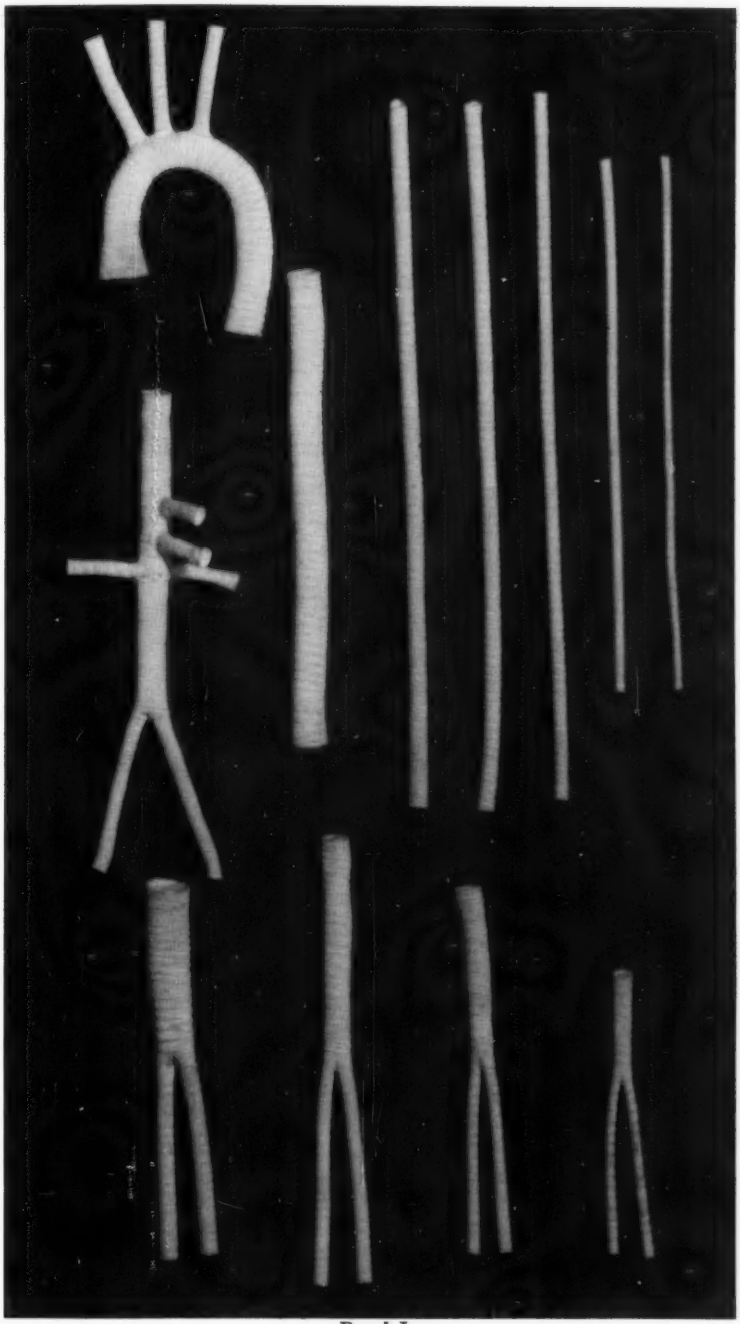


Panel I

This panel shows the various types and sizes of the Dacron grafts for replacement of different anatomical segments of the aorta and peripheral arteries.

Fig. 1. — Angiocardiogram showing aneurysms involving distal part of ascending aorta and transverse arch, as indicated by drawing in inset.

Fig. 2. — Same case as in Figure 1 showing method of resection of aortic arch and Dacron graft replacement. Drawings in upper part of Figure illustrate operative procedure using Dacron grafts for temporary bypass to maintain aortic and cerebral circulation during excision and graft replacement and subsequent conversion into the permanent graft. Photograph in lower part of Figure made at operation shows completed procedure.

Fig. 3.—*(a)* Drawing showing method of temporary bypass from ascending to descending aorta using Dacron graft for maintaining aortic circulation during excision and graft replacement of a fusiform aneurysm of transverse arch of aorta. *(b)* Drawing showing completed procedure with Dacron graft replacement of excised segment of transverse arch and with restoration of continuity to left subclavian artery.

Fig. 4. — Photograph made at operation in same case as in Figure 3 showing completed procedure of resection with replacement by Dacron graft, including anastomosis to left subclavian artery and use of bypass Dacron graft from ascending to descending aorta.

Fig. 5. — Angiocardiogram of patient with dissecting aneurysm of descending thoracic aorta showing characteristic double aortic lumen produced by relative difference in concentrations of dye in true and false aortic lumens, as depicted in diagram in inset.

Fig. 6. — Photograph made at operation in same patient as in Figure 5 showing completed replacement of the segment of aorta and dissecting aneurysm with Dacron grafts.

Fig. 7. — Angiocardiogram in same patient as in Figures 5 and 6 made approximately seven months after operation, showing relatively normal outline of thoracic aorta. Patient has been completely relieved and has resumed normal activity.

Fig. 8. — Photograph of sagittal section of resected segment of dissecting aneurysm in same patient as in Figures 5 to 8, showing gross pathologic features of lesion, with arrow pointing to intimal tear through which true lumen communicated with false lumen.

Panel II

Fig. 1

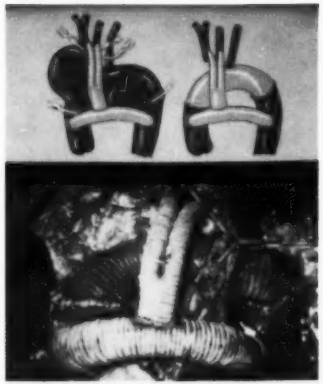


Fig. 2

Fig. 3

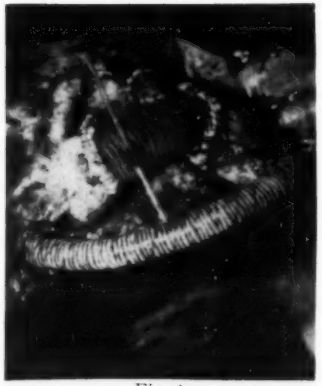


Fig. 4

Fig. 5

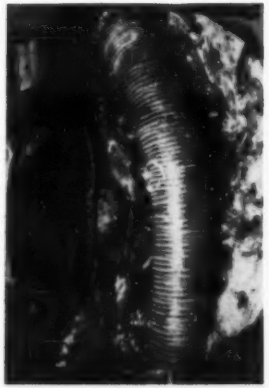


Fig. 6

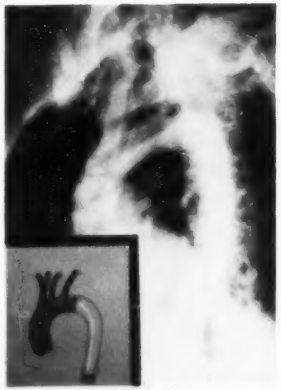


Fig. 7

Fig. 8

Panel II

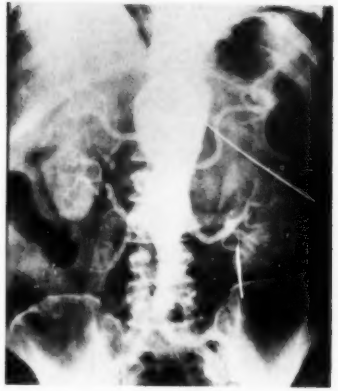


Fig. 1

Fig. 2

Fig. 3

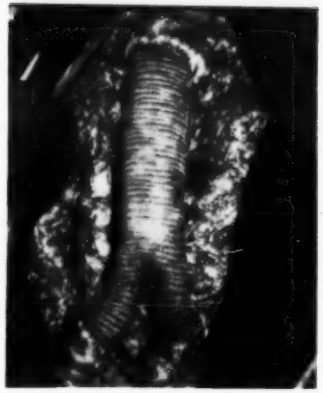


Fig. 4

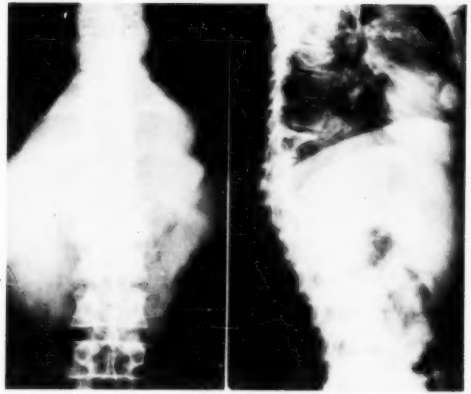


Fig. 5

Fig. 6

Fig. 7

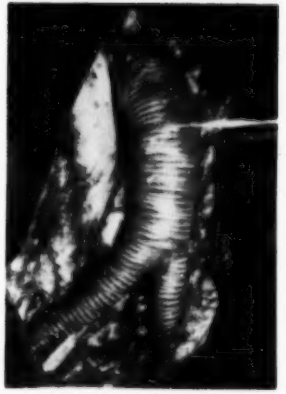


Fig. 8

Panel III

Fig. 1. — Aortogram showing fusiform aneurysm arising in distal segment of descending thoracic aorta and extending down to involve entire segment of abdominal aorta, including celiac, superior mesenteric, and renal arteries.

Fig. 2. — Photograph in same case as in Figure 1 made at operation, showing completed replacement of excised segment of thoracoabdominal aorta and aneurysm with Dacron graft, including branches to celiac, superior mesenteric, and both renal arteries. In the performance of this procedure the Dacron tube provides a significant advantage in that it permits conversion of the Dacron graft used first as a temporary shunt into the subsequent permanent graft.

Fig. 3. — Photograph made at operation showing characteristic appearance of an arteriosclerotic aneurysm of the abdominal aorta, arising just below the origin of the renal arteries and extending down to involve the bifurcation.

Fig. 4. — Photograph made at operation in same patient as in Figure 3 showing completed procedure following resection of aneurysm and replacement with bifurcation Dacron graft.

Fig. 5. — Roentgenograms of chest of patient showing mass in upper abdomen and lower mediastinum causing bone erosion, produced by syphilitic aneurysm of aorta.

Fig. 6. — Photograph in same case as in Figure 5 made at operation, showing completed replacement of excised segment of aorta and syphilitic aneurysm by means of Dacron graft.

Fig. 7. — Aortogram of patient with Leriche syndrome showing partial occlusion of the distal abdominal aorta and bifurcation with involvement of both common iliac arteries.

Fig. 8. — Photograph made at operation showing use of bifurcation Dacron graft in application of bypass principle in treatment of patient in Figure 7. The Dacron graft is attached by an end-to-side anastomosis to the abdominal aorta above and the external iliac artery below, thus bypassing the occlusive lesion.

Panel III

Fig. 1. — Photograph made at operation showing application of bypass principle using Dacron graft in a patient with extensive occlusive disease involving terminal abdominal aorta and both common and external iliac arteries. The trunk of the bifurcation tube is attached as an end-to-side anastomosis to the abdominal aorta, and both limbs of the bifurcation tube are brought down through the femoral canal and attached as an end-to-side anastomosis to both common femoral arteries, thus bypassing the occluded segment.

Fig. 2. — Photograph made at operation, along with drawing illustrating use of Dacron grafts in application of two principles of therapy, namely, excision with graft replacement and the bypass procedure. The bifurcation Dacron tube was used to replace the terminal abdominal aorta and iliac arteries. The presence of an associated segmental occlusion of the right superficial femoral artery necessitated application of the bypass graft attached by an end-to-side anastomosis to the abdominal aortic graft and extending down to be attached as an end-to-side anastomosis to the popliteal artery below the occlusion.

Fig. 3. — Photograph made at operation showing end-to-side anastomosis between common femoral artery and Dacron tube to bypass occlusion of superficial femoral artery.

Fig. 4. — Photograph made at operation in same patient as shown in Figure 3 showing lower end-to-side anastomosis of Dacron tube to popliteal artery.

Fig. 5. — Arteriogram showing aneurysm of common femoral artery and segmental occlusion of superficial femoral artery.

Fig. 6. — Photograph and drawings of same case as in Figure 5, illustrating findings at operation and showing aneurysm of common femoral artery with segmental occlusion of superficial femoral artery.

Fig. 7. — Photographs and drawings showing method of treatment using Dacron graft in case shown in Figures 5 and 6. The Dacron tube is attached as an end-to-end anastomosis to the external iliac artery following resection of the aneurysm with the deep femoral artery attached to the tube as an end-to-side anastomosis and with the tube brought down to be attached as an end-to-side anastomosis to patent popliteal artery below occlusion.

Fig. 8. — Arteriogram of patient shown in Figures 5-7 following operation, showing functioning Dacron graft.

Panel IV

Fig. 4

Fig. 3

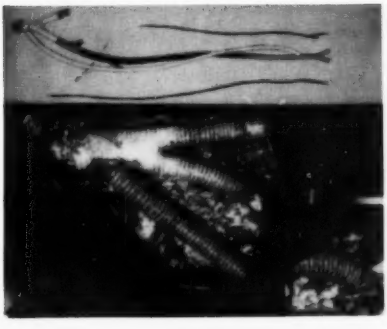


Fig. 2

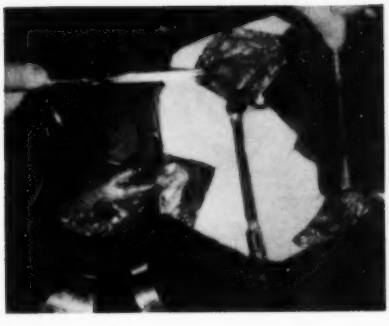


Fig. 1

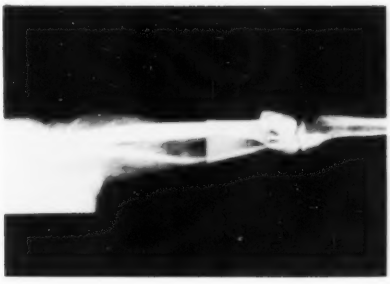


Fig. 8

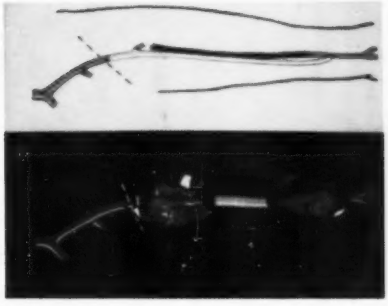


Fig. 7

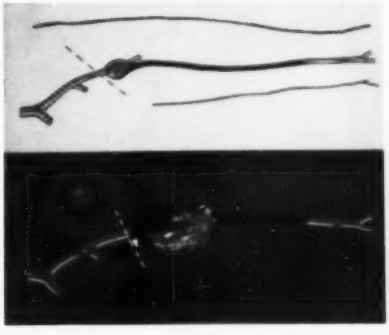


Fig. 6

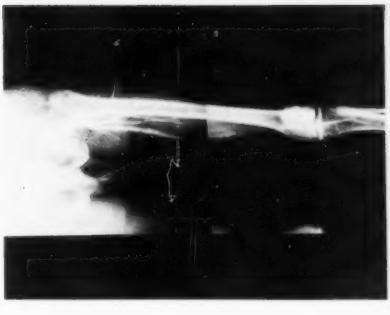


Fig. 5

Panel IV

Fig. 1. — Angiocardiogram of patient with segmental thrombo-obliterative disease of branches of aortic arch (other terms include aortic arch syndrome, pulseless disease, or Takayasu's disease), showing complete occlusion of innominate artery and partial occlusion of left common carotid artery, as depicted by drawing in inset.

Fig. 2. — Drawing illustrating surgical procedure employed in treatment of patient shown in Figure 1, using trifurcation Dacron tube to bypass occlusion in innominate and left common carotid arteries.

Fig. 3. — Photographs made at operation in same case as that in Figures 1 and 2, showing, in lower portion, attachment of Dacron tube as an end-to-side anastomosisto ascending aorta and, in the upper part of the photograph, the three branches of the Dacron tube, shown through a collar incision in the neck. The tube on the right extends to the left common carotid artery to be attached as an end-to-side anastomosis. The center tube is shown attached as an end-to-side anastomosis to the right common carotid artery, and the tube on the left is extending out to be attached as an end-to-side anastomosis to the right subclavian artery.

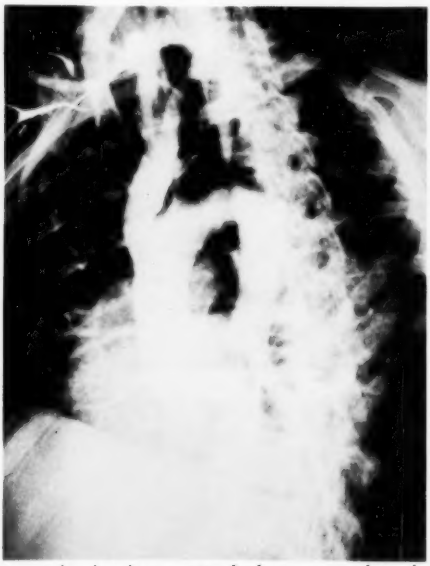


Fig. 4. — Angiocardiogram made after operation in case shown in Figures 1-3, showing functioning trifurcation Dacron tube and restoration of normal circulation.

Fig. 1. — Photographs made at operation through five separate incisions, showing bypass bifurcation Dacron graft extending from abdominal aorta above to both common femoral and popliteal arteries below in treatment of extensive segmental occlusive disease of terminal abdominal aorta and femoral arteries.

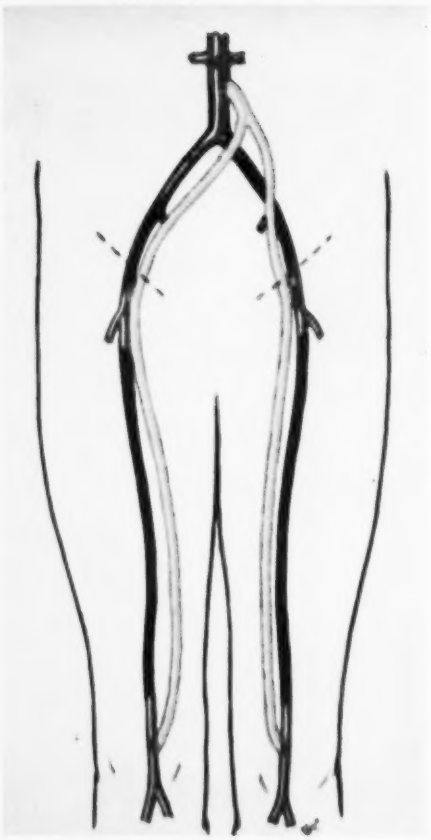


Fig. 2. — Drawing illustrating extent of occlusive disease and use of bypass Dacron graft in treatment of patient shown in Figure 1.

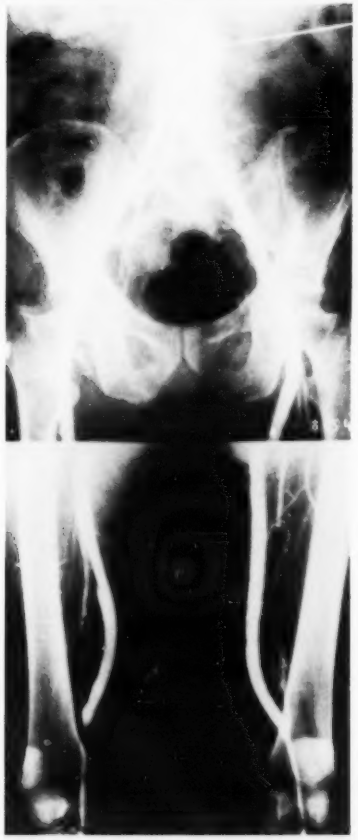
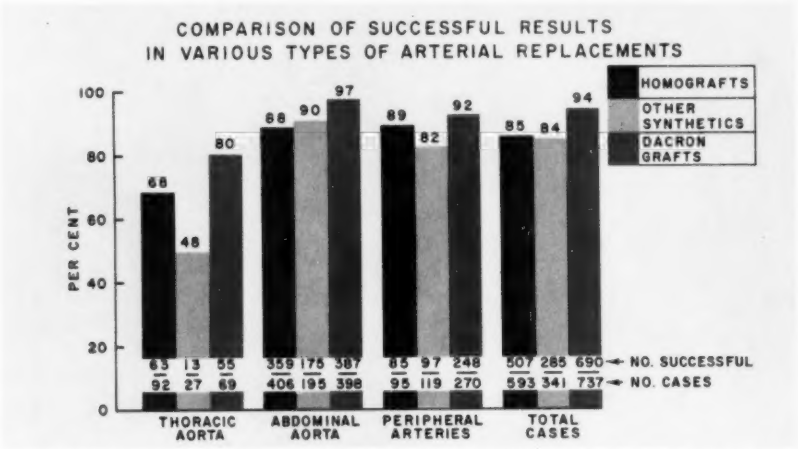


Fig. 3. — Aortogram made after operation in patient shown in Figures 1 and 2, showing restoration of normal circulation by means of the bypass Dacron graft.

RESULTS

DACRON GRAFTS	NUMBER CASES	DEATHS	GRAFT FAILURES	SUCCESSFUL
THORACIC AORTA				
ANEURYSMS	51	13(25%)	0	38(75%)
OCCLUSIONS	18	1(5.5%)	0	17(94%)
ABDOMINAL AORTA				
ANEURYSMS	235	6(2.6%)	1(0.4%)	228(97%)
OCCLUSIONS	163	1(0.6%)	3(2%)	159(98%)
PERIPHERAL ARTERIES				
ANEURYSMS	27	2(7%)	1(4%)	24(89%)
OCCLUSIONS	243	2(0.8%)	17(7%)	224(92%)
TOTAL DACRON GRAFTS	737	25(3.4%)	22(3%)	690(94%)
TOTAL OTHER SYNTHETIC GRAFTS	341	29(8%)	27(8%)	285(84%)
TOTAL HOMOGRAFTS				
TOTAL ALL GRAFTS	1671	116(7%)	73(4%)	1482(89%)



Tabulation and graphic representation of results obtained from an analysis of our experience with 737 cases in which the Dacron graft was employed for the treatment of various forms of aortic and arterial diseases. A comparison of these results with those obtained in our previous experience with the use of other types of synthetic vascular replacements and with homografts indicates the Dacron graft to be superior in all respects. Both the mortality and the incidence of failures attributable to grafts were significantly lower in the Dacron series.

Prolapse of a Megarectum

PAUL B. DARON, M.D., and H. ALLEN KING, M.D., Shreveport, La.

Megarectum, unassociated with dilatation of the proximal bowel, is a rare anomaly. Two such cases,[1,6] each in children with imperforate anus, are recorded.

Prolapse of a megarectum in an adult with a normally functioning anus and no other bowel anomaly is, we believe, a unique occurrence.

From the Surgical Service, Veterans' Administration Hospital.

The pathologic examination and report, with photomicrographs showing the significant histology of the sigmoid colon, were prepared by Major John H. Draheim (MC), U. S. Army, of the Armed Forces Institute of Pathology, Washington, D. C.

Fig. 1.—Megarectal prolapse. The entire thick and glistening rectal mucosa is everted through a completely relaxed anus. No embarrassment of circulation is apparent. The rectosigmoid, leadpoint of the intussusceptum, appears as a dimple in the most dependent portion.

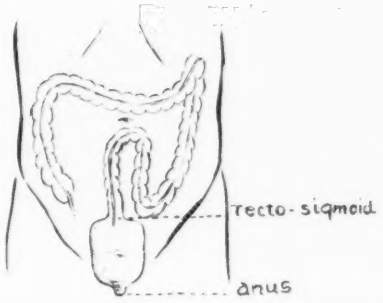


Fig. 2.—Megarectum. The long sigmoid colon terminates sharply in a wide rectal sac.

Report of a Case

A 56-year-old Negro man, while straining during passage of a loose stool, suddenly had prolapse of an enormous rectal mass. This had never previously happened, and he had experienced no bowel dysfunction other than unexplained diarrhea during the past three years, when occasionally four

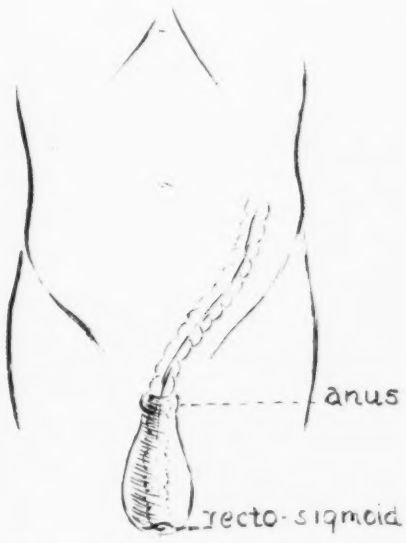


Fig. 3.—Mechanism of prolapse. The rectosigmoid has traversed the entire rectum, prolapsing and everting it through the relaxed anus.

Fig. 4. — Megarectum. The enormous, presently empty rectum, filling the entire pelvis, has been loosely grasped with forceps to demonstrate the rectosigmoid.

or five loose stools were passed daily, without rectal bleeding, pain, or tenesmus.

Examination revealed massive prolapse with complete eversion of a large, thick-walled rectum (Figs. 1 and 3). The anal sphincter was, fortunately, completely relaxed, so that there was no embarrassment of the blood supply. The rectosigmoid junction appeared at the most dependent portion, and, at irregular intervals, peristalsis was seen.

An attempt was made to reduce the mass after administration of morphine, but was unsuccessful. Since the bowel was relaxed, viable, and not obstructed, preparatory management with saline compresses was decided upon.

Reduction was later accomplished with some difficulty under low spinal anesthesia, after which the patient was confined in bed for preoperative preparation, with his buttocks strapped tightly together, except for defecation.

Figure 5

Fig. 5.—Megarectum. The long, redundant sigmoid has been completely mobilized and drawn upward. The posterior attachment of the upper rectum has been freed. Large, tortuous blood vessels may be seen in the anterior rectal wall.

Fig. 6.—Operative procedure. (*a*) The site selected for excision of the redundant sigmoid leaves a generous blood supply for the very large distal segment. (*b*) A longitudinal, antimesenteric incision extends from the distal sigmoid to the upper rectum.

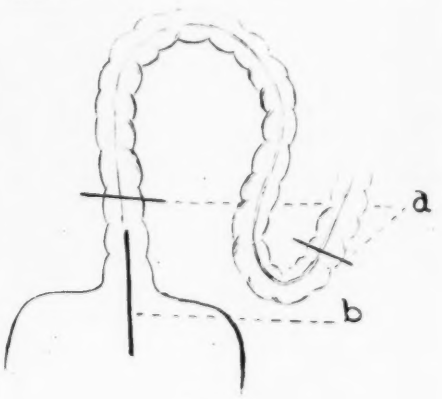


Figure 6

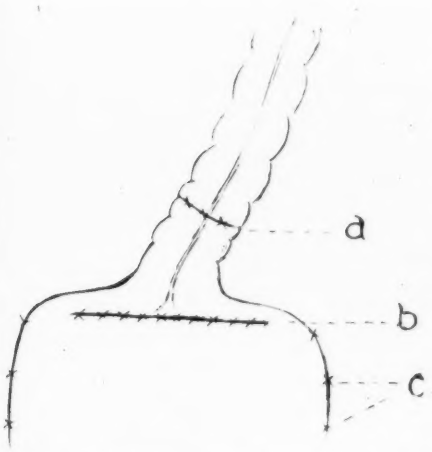


Fig. 7.—Completed operative procedure. (*a*) Site of anastomosis. (*b*) Transverse closure of the longitudinal incision through the rectosigmoid. (*c*) Suture of the rectum to the dense presacral fascia.

Operation.—Abdominal exploration disclosed an unusually long and redundant sigmoid colon, terminating in a massive rectum, which nearly filled the pelvis (Figs. 2 and 4). The latter organ was a thick, flabby receptacle, covered by pale serosa, through which large, tortuous blood vessels were seen.

The mesocolon was divided at the base, completely freeing the long sigmoid colon and exposing the ureters and blood vessels for identification. The pelvic peritoneum was opened on each side and an attempt made to mobilize the megarectum from its pelvic attachments (Fig. 5). Unexpected difficulty was encountered, due to dense posterior fibrous supporting bands. After mobilization of the uppermost portion, abdominoperineal resection, the first-planned procedure, was abandoned because of excessive operative risk.

The rectosigmoid was opened longitudinally along the antimesenteric border, extending the incision downward for a short distance upon the rectum (Fig. 6). The sigmoid appeared normal, but the bowel became sharply thickened at the rectosigmoid, its wall at this point comprising in depth, from the serosa, large, tortuous subserosal blood vessels, greatly enlarged smooth-muscle layers, very loose, areolar submucosa, and hypertrophied rectal mucosa.

The antimesenteric opening was closed transversely, considerably widening the rectosigmoid and lessening the possibility of recurrent intussusception, with this as the lead point (Fig. 7). The redundant sigmoid was resected a short distance above this site, leaving an adequate source of blood supply to the large rectum, and end-to-end anastomosis was done. The upper rectum was then firmly sutured to the thick presacral fascia and the peritoneum closed.

Postoperative Course.—Postoperative recovery was entirely uneventful, and normal bowel function returned after the third postoperative day.

Proctoscopic examination, accomplished some time later, disclosed the relatively enormous, but collapsed, rectal cavity. There was marked infolding of thick mucosa. The anal sphincter was relaxed, preventing satisfactory dilatation of the pouch to full capacity by air pressure. The recto-

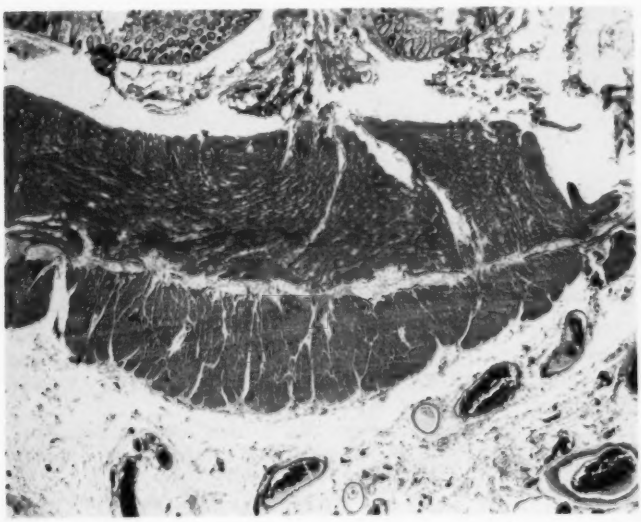


Fig. 8. — Photomicrograph of the sigmoid colon, showing a definite increase in size of the myenteric nerve plexus between the longitudinal and the circular muscle fibers. Hematoxylin-eosin stain; × 16.

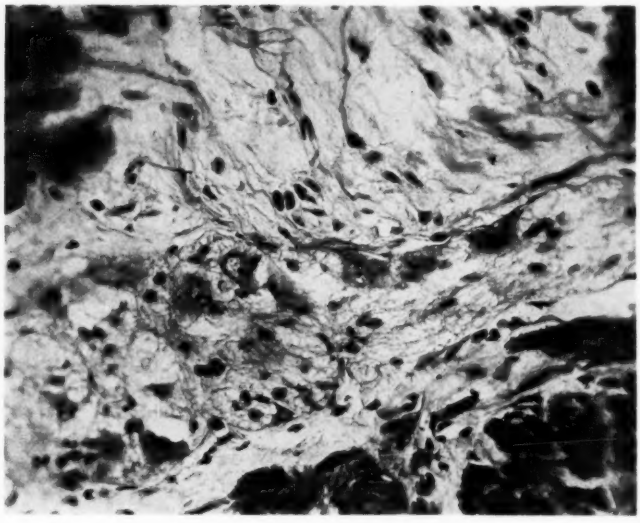


Fig. 9. — Photomicrograph of the sigmoid colon, showing an increase in the number of ganglion cells. Hematoxylin-eosin stain; × 305.

sigmoid junction was found as an opening, high on the left side of the large sac.

Follow-up barium studies confirmed these observations.

Histology.—The sigmoid colon, submitted for special histologic study,[3] was described as follows (Figs. 8 and 9):

"The sections of sigmoid colon show a marked increase of nerve fibers and probably an increase in the number of ganglion cells of the myenteric plexus; however, the individual fibers and cells appear normal. This change is sometimes seen proximal to the aganglionic segment of bowel in Hirschsprung's disease, and, according to some, must be considered abnormal. This change suggests that there is an imbalance between the autonomic nervous system of the sigmoid colon and that of the rectum."

Comment

This 56-year-old Negro man, without previous difficulty, suddenly had prolapse of a megarectum while straining during passage of a loose stool. The mechanism, obviously, was intussusception of a long sigmoid colon, the lead point being the rectosigmoid, which had traversed the rectal pouch and passed through the anus, everting the entire rectum. Fortunately, the anus was relaxed, allowing protrusion of this enormous mass without compromise of blood supply. This permitted reduction, preparation, and later selection of a relatively simple operative procedure.

Abdominoperineal resection was abandoned, because of exceptional technical difficulty. Resection of the sigmoid, opening and considerably widening the rectosigmoid, and firmly fixing the upper rectum to the pelvis posteriorly, was an apparently successful procedure.

In this case, the relaxed anus seems to rule out anal obstruction, either from spasm or from stricture, as a cause of megarectum.

Summary

Prolapse of a megarectum, unassociated with dilatation of the proximal bowel or anal obstruction, and first occurring in a 56-year-old man, is, we believe, a unique occurrence. The problem of management, reduction, and operative repair are discussed.

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Primary Multiple Cancers

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Primary multiple cancers are spoken of as synchronous when two or more originate simultaneously (or at an interval of about six months), and as metachronous when there is a long interval (more than six months) between appearances. The distinction can be made with some degree of accuracy on surface, or accessible, cancers but hardly ever on deep-seated, visceral cancers, because the clinical manifestations of the latter do not usually coincide with the actual appearance of the growth. Some visceral cancers produce symptoms early; others remain silent until late, sometimes until they have attained considerable size. In the series reported here metachronicity could be reasonably accepted in one case only.

Some authors have included in the category of multiple cancers the condition in which a cancer appeared *de novo* long after the (surgical) cure of a previously existing cancer. This series contains a similar case (Case 6).

Perhaps of greater significance than synchronism is the distinction between cancers of the same system and those of different systems. The combination of cancers of the same system, for example, the breast, cervix, and ovaries, may possibly be related to an endocrinologic factor.

Although primary multiple cancers were first described in the second half of the 19th century (by Billroth, in 1879), they remained virtually unknown until the mid-20's of this century. For example, in 1926 Siebke [1] was able to collect only 26 cases of primary double cancer, to which he added 2 of his own. Puhr,[2] in 1927, reported 6 cases disclosed in 1559 cases of cancer (0.3%) found in 6718 autopsies. In 1928 I [3] reported three cases. As my cases were found in a rather limited number of autopsies, I ventured the opinion that primary multiple cancers probably occurred with greater frequency than had been theretofore believed, but that they were usually either overlooked or unrecorded.

During the past three decades many articles on the subject have appeared in European, as well as American, literature. In a number of these reports authors included malignant tumors of different germinal layers, such as carcinoma and sarcoma (also other mesodermal tumors), and cutaneous cancers also were often included. It is well known that surface cancers are frequently multiple. A high incidence of multiple basal-cell cancers of the skin were reported by Schreiner and Wehr,[4] who found 76 multiple cancers in 307 cases of cutaneous cancers.

Material

In this paper I report on 24 cases of primary multiple cancers disclosed among 1514 visceral cancers found in 4800 consecutive autopsies. In 20 of these cases 2 primary cancers were found in each patient, and in 4 cases 3 were found. Of the total 1514 cancers, 818 (or 54%) were found in men and 698 (46%) in women. Of the 24 cases of multiple cancer, 15 occurred in men and 9 in women. Of 40 cases reported by Warren and Gates,[5] 15 occurred in men and 25 in women, and of 25 cases reported by Kirshbaum and Shively,[6] 17 occurred in men and 8 in women. The average age of my patients with two cancers was 61.5 years for men and 50 years for women. In Warren and Gates' cases, the average for

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men was 67.7 years and for women 58.2 years, and in Kirshbaum and Shively's cases, it was 66 years for the men and 57.2 years for the women. The average age of the four patients with three cancers was 62 years. Of six cases in which cancer of the lung was associated with cancers of other organs, three involved men and three women. Of the 20 double cancers, 6 were associated with a cancer of the lung, and of the 4 triple cancers, 1 was so associated.

Synopsis of Cases

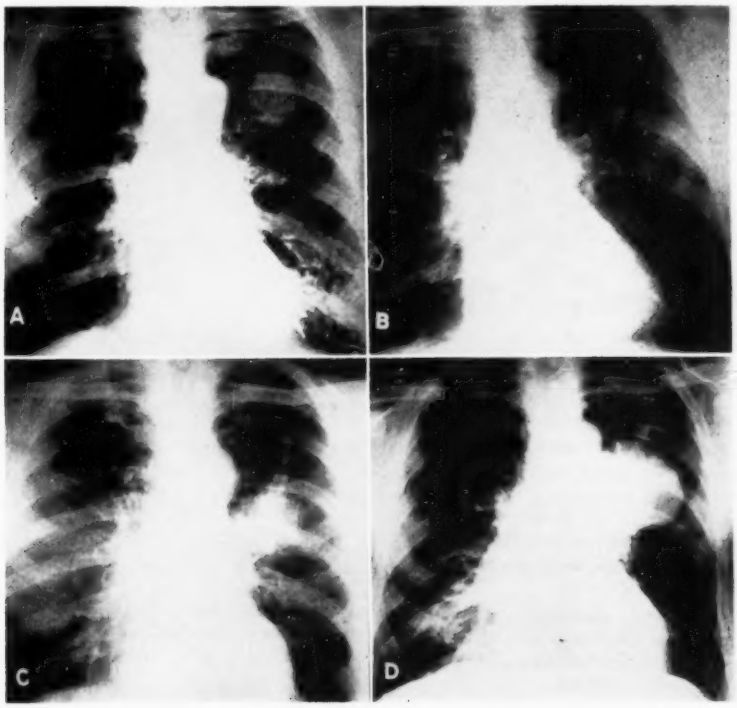
Triple Cancer

CASE 1.—A man of 64 complained of a productive cough, loss of weight, shortness of breath, and easy fatigue, as well as of frequent micturition. Examination of the lungs showed harsh breath sounds extending from the apex of the left lung to the fourth intercostal space. The breath sounds below that area were diminished. An x-ray examination showed a dense area in the upper portion of the left lung and an area of "unresolved pneumonia" (or bronchiectasis) at the base of the same lung (Fig. 1*A*). There was no evidence of tuberculosis. The laboratory data were noncontributory. The diagnosis was cancer of the upper lobe of the left lung.

In a period of 18 months the patient received 233,000 mc.-hr. from an element pack. Examination at the end of treatment showed no evidence of the mass (Fig. 1*B*). The patient remained well for about two years, after which he complained of dysuria, frequency, and hematuria. Examination disclosed a carcinoma of the prostate. Simultaneous x-ray examination of the chest revealed the reappearance of the tumor in the upper left lobe (Fig. 1*C* and *D*). The patient began to deteriorate rapidly. The cough which had troubled him at the onset of the illness became severe and the expectoration abundant. His temperature rose and remained elevated. He died six years after the diagnosis of cancer of the lung was made.

Autopsy revealed a necrotic bronchiogenic cancer, about 10 cm. in diameter, replacing the posterior

Fig. 1 (Case 1).—Primary triple cancer. *A*, x-ray taken on admission of the patient to the hospital. *B*, x-ray taken 20 months after admission. The almost complete disappearance of the tumor must be noted. *C*, x-ray taken about two years after *B*. The reappearance of the tumor must be noted. *D*, x-ray taken about six years after the patient's admission to the hospital.



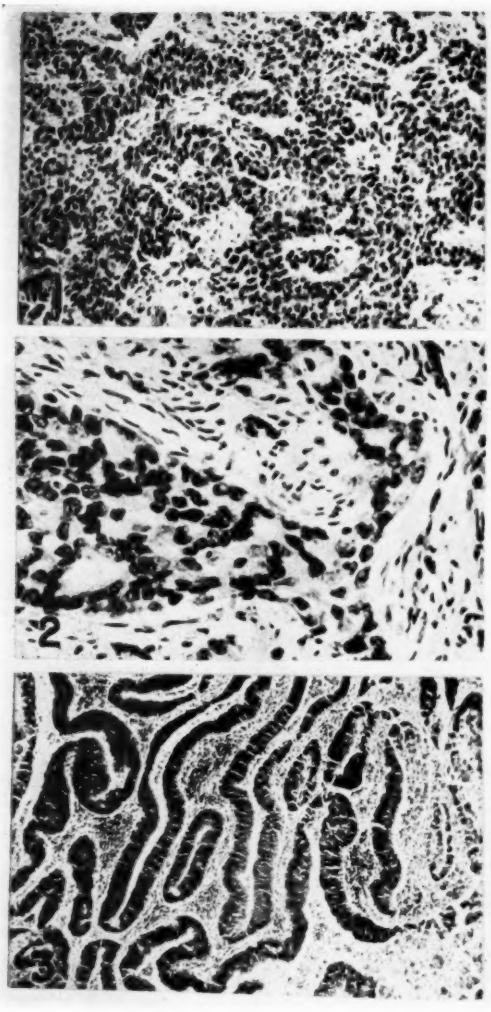


Fig. 2 (Case 1).—Primary triple cancer. *1*, oat-cell cancer of the lung; *2*, adenocarcinoma of the prostate; *3*, carcinoma of the large bowel.

half of the left lung. The tumor was well demarcated by a thick fibrous band at the interlobar fissure. The hilar lymph nodes showed the presence of tumor, but no metastases were found elsewhere.

Microscopically, the lung tumor was an undifferentiated oat-cell carcinoma (Fig. 2), and the prostate was infiltrated by adenocarcinoma (Fig. 2). Of the many polyps found in the large intestine, the largest, located in the descending colon, contained cancer (Fig. 2).

A tuberculous cavity was found at the base of the left lung and the tuberculous bronchopneumonia in the upper lobe. Miliary tubercles were scattered throughout both pulmonic fields.

Case 2.—Eighteen months after a radical mastectomy in a woman of 63, vaginal bleeding appeared, and a diagnosis of carcinoma of the uterus was made. At autopsy an adenocarcinoma of the endometrium was found, as well as carcinomatous transformation of a polyp of the sigmoid. Neither cancer showed metastases.

Case 3.—A man of 68 had complained of persistent abdominal pain for about a year and of intense pain in the back of a few months' duration. He had been examined in several hospitals without a diagnosis being made. At autopsy carcinoma of the body of the pancreas was found, metastatic to the liver and to the retroperitoneal

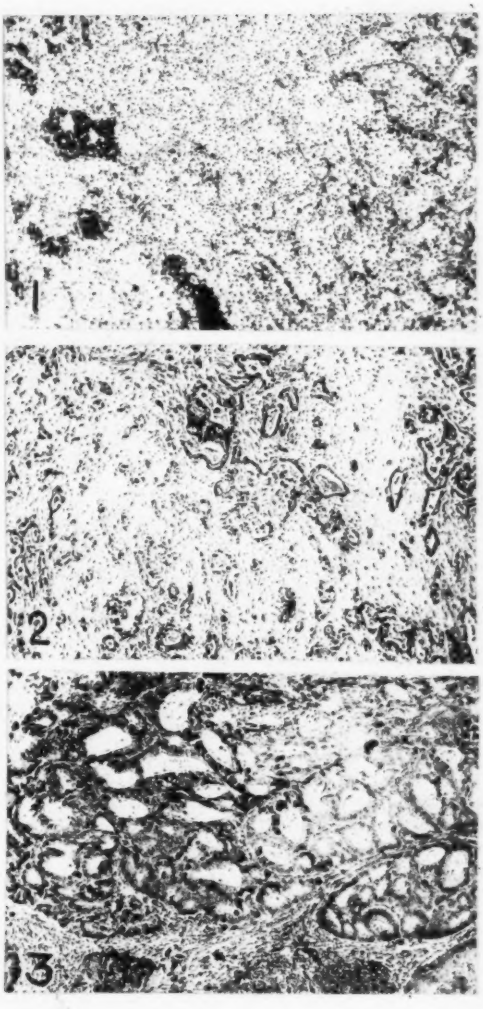


Fig. 3 (Case 3).—Primary triple cancer. *1*, hypernephroma; *2*, adenocarcinoma of the pancreas; *3*, carcinoma of the rectum.

tissue. The autopsy also revealed carcinoma of the colon and a hypernephroma, with no metastases from either cancer (Fig. 3).

Case 4.—A woman of 51 underwent a radical mastectomy for carcinoma of the right breast. Two years later hemiplegia developed. At autopsy a carcinoma of the uterus and an early carcinoma of the left breast were found. There was a solitary metastasis, from the breast, in the corpus callosum.

Comment.—In Case 1 the pulmonary disease absorbed the interest of the clinician, while the initial urinary symptoms were disregarded. No doubt, had the prostate been investigated as thoroughly as were the lungs, a cancer of the prostate would have been discovered simultaneously with that of the lung. The two cancers, i. e., of the lungs and of the prostate, should then be regarded as probably synchronous. The intestinal cancer was an incidental autopsy finding.

It is noteworthy that in the same case the usually radioresistant oat-cell cancer melted away under the influence of radia-

tion, only to reappear two years later. Post mortem, the pulmonary mass was seen to be walled off and had metastasized to the tributary lymph nodes only. As a rule, oat-cell cancers metastasize widely. The prostatic and rectal cancers showed no metastases.

In Cases 1 and 3 the cancers developed in organs of different systems. In Case 2 two cancers developed in organs of the same system, i. e., the breast and the uterus, while the third cancer was in an organ of a different system (the colon). In Case 4 the cancers developed in organs of the same system.

Double Cancer of Different Systems

CASE 5.—In this case, a woman of 75 had been ill about six months with a "cold," aggravated by intense pain in the neck and abdomen. An x-ray examination of the chest revealed a carcinoma of the right upper-lobe bronchus. At autopsy the pulmonary cancer showed metastases to the cervical lymph nodes, the liver, and the left adrenal. A carcinoma of the stomach with metastases to the liver was an incidental finding.

CASE 6.—A woman of 55 complained of persistent pain in the abdomen, irregular bowel movements, and constipation. The clinical diagnosis was carcinoma of the rectum. At autopsy the rectal cancer showed extension to the pelvic tissue and to the posterior wall of the cervix. A carcinoma of the bronchus was also discovered, with metastases to the lymph nodes, pancreas, adrenals, omentum, and rectum. *A metastasis from the pulmonary cancer was found in the midst of the rectal cancer.*

CASE 7.—A woman of 46 complained of pain in the lower back. The x-ray disclosed a cancer of the lower lobe of the left lung. There was generalized lymphadenopathy caused by neoplastic infiltration, and a tumor mass in the left supraclavicular fossa. The woman died six months after the onset of symptoms. At autopsy an adenocarcinoma of the lungs was found, with metastases to the contralateral lung, pericardium, left adrenal, broad ligament, and liver. There was also a hypernephroma, which did not metastasize.

CASE 8.—A man of 71 complained of pain in the chest, cough, and blood-streaked sputum, which had started about five years after resection of the bowel for carcinoma. An x-ray examination of the chest revealed a cancer of the lower lobe of the left lung. The intestinal cancer, which had been resected five years previously, showed no recurrence.

CASE 9.—A man of 49 had suffered from asthma for many years. About six years before his admission to the hospital he began to feel sharp pains in the chest, weakness, which grew steadily in intensity, and noted a gradual loss of weight. At autopsy a bronchiogenic carcinoma of the left main bronchus was found, metastatic to the lymph nodes, and a carcinoid of the small intestine.

CASE 10.—The onset of symptoms in this woman, aged 36, dated back about six months before clinical attention. She complained of vague but persistent pain in the lower abdomen. Exploratory laparotomy disclosed a bilateral ovarian cancer, which was removed. Death ensued four months later. Autopsy revealed an ovarian cancer, with peritoneal metastases, and carcinoma of the sigmoid colon, with metastases to the regional and peritoneal lymph nodes and to the liver.

CASE 11.—A woman of 60 complained of low-back pain and loss of weight of about six months' duration. The clinical diagnosis was carcinoma of the kidney. The autopsy revealed a renal cancer, with metastases to the visceral organs and the skeleton, and carcinomatous transformation of a polyp in the sigmoid colon.

CASE 12.—A man of 77 had complained of intestinal irregularities and of a steady loss of weight for two years. Shortly before death he became aware of hoarseness. He died a few weeks after admission to the hospital. At autopsy an adenocarcinoma of the rectum was found, as well as a squamous-cell carcinoma of the larynx.

CASE 13.—A woman of 66 noticed that a "lump" which had been in her breast for 13 years had become greatly enlarged. Examination revealed a carcinoma which replaced almost the entire breast, with metastases to the axillary lymph nodes. A radical mastectomy was performed. She died three years later. The autopsy revealed local recurrence of the mammary cancer and a carcinoid of the ileum (Fig. 4).

CASE 14.—The illness of a man of 77 started with an intense pruritus and painless jaundice a few months prior to his hospitalization. He died shortly after admission to the hospital. The autopsy revealed a carcinoma of the ampulla of Vater, obstructing the common bile duct, and also a hypernephroma with no metastases (Fig. 5).

CASE 15.—A carcinoma of the tonsil was found in a man of 69, and radiotherapy was applied, with no improvement. The autopsy confirmed the diagnosis of a tonsillar cancer. In addition, a carcinoma of the prostate with no metastases was found.

CASE 16.—A man of 87 showed symptoms compatible with a pancreatic cancer, which had existed about four years. For the previous two years he had suffered from urinary disturbances. At autopsy a carcinoma of the head of the pancreas with metastases to the liver was found. There was

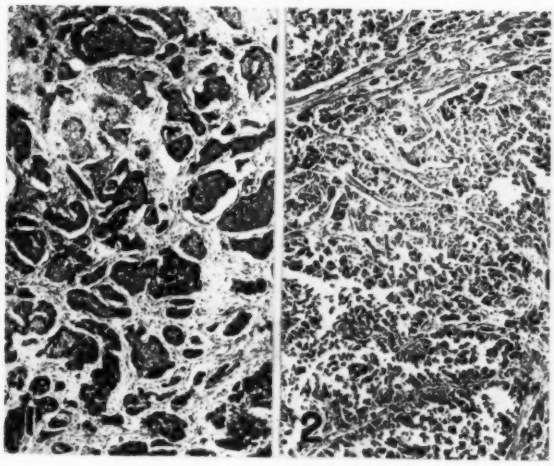


Fig. 4 (Case 13).—Primary double cancer. *1*, carcinoma of the ileum; *2*, carcinoma of the breast.

also a carcinoma of the prostate with extension to the bladder and to the seminal vesicles.

Case 17.—A woman of 57 complained of vaginal bleeding of two years' duration. A panhysterectomy disclosed a carcinoma of the endometrium, with no invasion of the neighboring tissue or the lymph nodes. She was well for about three years, when cancer of the tonsil was found, with metastases to the liver, bile ducts, gallbladder, spleen, and adrenals. There was no evidence of the uterine cancer.

Case 18.—A woman of 68 had suffered from dysphagia for about three years. A carcinoma of the thyroid gland with extension into the adjacent tissue was found. Radiation therapy was to no avail, and she died within a few months. The autopsy revealed a papillary adenocarcinoma of the thyroid, with invasion of the adjacent tissue, and a hypernephroma with metastases to the lungs, pleurae, adrenals, diaphragm, and thyroid.

Double Cancer of the Same System

Case 19.—For this woman of 71 the clinical diagnosis was carcinoma of the colon, and a laparotomy was performed. At autopsy a bilateral papillary-cyst adenocarcinoma of the ovary was found, with invasion of the pelvis and metastases to the bronchial and abdominal lymph nodes, peritoneum, intestine, liver, and spleen. There was also carcinoma of the cervix, with extension to the corpus uteri, vagina, and pelvis.

Case 20.—The clinical diagnosis for this woman of 53 was carcinoma of the breast and the cervix. A radical mastectomy and a panhysterectomy were performed, followed by intense radiation therapy.

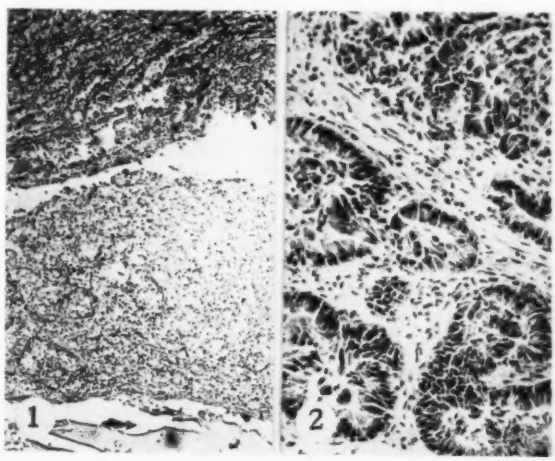


Fig. 5 (Case 14).—Primary double cancer. *1*, hypernephroma; *2*, carcinoma of ampulla of Vater.

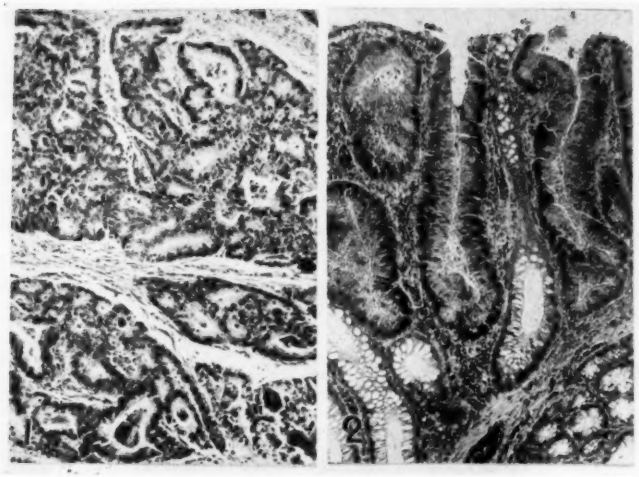


Fig. 6 (Case 23).—Primary double cancer. *1*, carcinoma of the rectum; *2*, carcinomatous transformation of a rectal polyp.

The patient died three and one-half years after the operation. Autopsy revealed recurrence of the cervical cancer, with metastases to the pelvis and the liver. There was no evidence of the mammary cancer.

Case 21.—Intestinal obstruction signaled the onset of symptoms in a woman of 30. At the exploration a cyst adenocarcinoma of the ovary was found and resected. Eight months later vaginal bleeding appeared, and a cancer of the cervix uteri was discovered. At autopsy the cervical cancer with metastases was identified, but no evidence of the ovarian cancer was disclosed.

Case 22.—A radical mastectomy was performed on a woman of 32 who had noticed a "lump" in her breast eight months before. She died 16 months later. Autopsy showed widespread metastases from the mammary cancer and a cyst adenocarcinoma of both ovaries, with no metastases.

Case 23.—A woman of 52 had suffered from intestinal disturbances for about 18 months, when a colostomy was performed. She died six months later. At autopsy an adenocarcinoma of the rectum was found, and also a carcinomatous transformation of a polyp of the sigmoid colon (Fig. 6).

Case 24.—For a man of 80 a diagnosis of cancer of the rectum was made, and a colostomy was performed. He died six months later. At autopsy carcinoma of the rectum was found, as well as carcinoma of the cardiac end of the stomach.

Comment.—Of the 20 double cancers, 13 arose in organs of different systems, and 7 took origin in organs of the same system. It is noteworthy that in 10 of the 24 cases 1 of the cancers originated in the large bowel. In 6 of the 24 cases 1 cancer was bronchiogenic.

At the Memorial Center, New York, of 1493 cases of cancer of the lung, there were 25 in which the tumor was one of two or more separate primary malignant growths, an incidence of 1.6%. According to Cahan,[7] there have been at least 37 reported cases in which, at autopsy, a cancer of the lung has been found to be one of two malignant tumors. There was but one primary triple cancer.

Warren and Gates[5] found 120 lung cancers in their autopsies, 9 of which were associated with another primary cancer, an incidence of 7.5%. The 6 cases of pulmonary cancer associated with one or two other cancers, reported in this article, were found in 212 autopsies on patients with bronchiogenic cancer, an incidence of 2.83%.

The cancer most frequently associated with another cancer was cancer of the large bowel, followed by cancer of the lung, cancer of the kidneys, and cancer of the breast.

Attention has been drawn to the frequent association of bronchiogenic cancer and laryngeal cancer.[8-10] Thomson and Schaff,[8] in a series of 20 cases of cancer of the larynx observed at autopsy, found 5 cases

in which cancer of the larynx had developed concomitant with or subsequent to the cancer of the lung. In 3 of the 20 patients with laryngeal carcinoma, the laryngeal and the bronchial cancers were diagnosed either simultaneously or within a short interval of time. In two cases the laryngeal cancer preceded the bronchial cancer, one by seven months and the other by seven years. Cahan and his associates, in their study of the 1493 cases of cancer of the lung, mentioned above, found 4 synchronous laryngeal cancers, and Warren and Ehrenreich [11] found 2 cases of laryngeal and pulmonary cancers in 194 cases of multiple cancers. In none of my patients with cancer of the lung was a cancer of the larynx found. In one case (Case 12) cancer of the larynx was associated with cancer of the large bowel. Like cancer of the bronchus, cancer of the larynx has been linked to smoking.

General Comment

A study of 1514 cancers found in 4800 autopsies revealed 24 instances (1.58%) of primary multiple cancers. The incidence approximated the figures of Kirshbaum and Shively [6] at the Cook County Hospital, Chicago, who found 1.77% in 1411 cancers, and those of Goriainowa and Schabad,[12] who found 1.8% in 1238 cancers. Warren and Gates,[5] on the basis of American statistics, found an incidence of primary multiple cancers in 3.9% of cases, and, on the basis of their own series of 1078 cases, found an incidence of 3.7%. From a compilation of all available statistics, the incidence amounted to 1.89%.

It may be seen that while primary multiple cancers occur more frequently than has hitherto been reported, they are nevertheless rare. In man cancer is almost always solitary. Writers on the subject of primary multiple cancers have often stressed their frequency, and debate has centered on whether the multiplicity is a mere coincidence or is dependent on a susceptibility to epithelial malignant disease. Many observers have emphasized the theory that multiple cancers occur with greater frequency than chance alone can explain. They adhered to the concept of Verneuil,[13] who wrote, in a paper published in 1884, that in cases of primary multiple cancers their bearers were affected by *une aptitude morbigène constitutionelle. . . une diathèse néoplasique.* Warren and Gates wrote: "An individual with one cancer is more apt to develop a secondary cancer than he would be expected to do by chance alone." This implies, according to the authors, "predisposition or susceptibility to cancer in certain persons." A similar view was also expressed by Hurst and Broders,[14] who found 71 primary multiple malignant neoplasms in 2124 patients with cancer, an incidence of 3.4%. These authors wrote [14]:

> The multiple tumors that occur in different organs suggest a tumor diathesis in the individual, certainly a greater degree of susceptibility than can be explained away as mere coincidence or accident.

Other observers (also on the basis of statistical data) have reached the conclusion that the presence of two cancers in the same person does not signify a predisposition *sui generis* to the development of cancer. Watson,[15] from an analysis of the cases at the Memorial Center, New York, concluded that there is no constitutional predisposition to multiple cancers of different systems. Mider and his associates,[16] too, wrote: "The risk of developing a second cancer in a different organ or tissue from the one first affected was neither increased nor decreased by the presence of a primary malignant neoplasm of the sites studied."

The singleness of cancer in man is so impressive that it, rather than the plurality (which occurs in less than 2% of cases), is of compelling interest. The suggestion has been made that a kind of resistance may be at play; i. e., a person with one cancer possibly resists the development of another cancer.[3]

The British observers, Bashford,[16a] Murray,[16b] and others, showed that animals in which tumors had developed and then had been absorbed were highly refractory to subsequent inoculations. Likewise, animals

in which tumor had disappeared following exposure to radium were as refractory as those in which absorption had occurred spontaneously. Murray found that the induction of a new tumor after the first had been established met with intense resistance.

Besredka [16c] demonstrated that resistance can readily be induced. He used Brown-Pearce squamous-cell carcinoma, which is invariably fatal when the testicle of the rabbit is inoculated with the tumor. He found that when the malignant growth was inoculated intracutaneously, it became absorbed without inducing cancer. The animal in which the cancer was absorbed acquired a lasting resistance to subsequent inoculations with the same cancer, irrespective of organ or structure utilized for inoculation.

Greene and Strauss [17] have reported their observations, extending over a period of 17 years, on a colony of 1100 female rabbits. Of these, at autopsy 55 showed primary multiple cancers. The authors noted that the tendency to develop a second cancer was no greater in the affected animals than the tendency to develop one cancer in the unaffected animals. They also observed that the presence of one cancer had an inhibiting effect on the development of another cancer. In their opinion, an immunological factor was probably at play. "It seems probable," they wrote, "that in man as well as in the rabbit, the presence of one focus of neoplasia retards the development of the cancer." To be sure, no test is available to ascertain this conjecture. Perhaps in this respect the incidence of metastases in cases of primary multiple cancer may be of interest. In Case 1, concerning triple cancer, the usually widely metastasizing oat-cell cancer of the lung metastasized to the lymph nodes only (after a protracted course of over six years), while the prostatic cancer and the cancer of the colon failed to show metastases. In Case 7 the bronchial cancer metastasized, while the renal cancer (hypernephroma) did not. In Case 9, pertaining to carcinoid of the small intestine and bronchiogenic cancer, the pulmonary cancer metastasized to the lymph nodes only. In Case 12 neither the rectal nor the laryngeal cancer produced metastases. In Case 13, regarding cancer of the ampulla of Vater and a hypernephroma, no renal metastases were disclosed. In Case 15, neither the tonsillar nor the prostatic cancer showed metastases. In Case 21, the cervical cancer metastasized, while the ovarian did not. In Case 22, the mammary cancer showed metastases, while the ovarian cancer yielded none. In Case 23, neither the adenocarcinoma of the rectum nor the cancer of the sigmoid colon had metastasized. Finally, in Case 24, no metastases were produced by the gastric cancer or by the cancer of the large bowel.

Metastasis of Cancer to Cancer.—In 1 of the 24 multiple cancers, a bronchiogenic cancer metastasized to a cecal cancer (Case 6).

Rabson and his associates [18] were able to collect from the literature 19 cases of metastasis from one cancer to another. To this number they added five of their own. The fact that so many cases were discovered in one institution would indicate that the condition is not so rare as is commonly believed. Two more cases (not included in this series) have been observed by me. In one, a bronchiogenic cancer metastasized to a giant-follicle lymphoblastoma, and in the other, to a meningioma.

Case 25.—In the first case a man of 69 developed an adenopathy in the supraclavicular fossae, left axilla, and left groin. There was splenomegaly, and the hemogram showed leukemia. A biopsy of an axillary lymph node showed giant-follicle lymphoblastoma invaded by adenocarcinoma (Fig. 7). Roentgen-ray studies failed to reveal the primary seat of the cancer. Within the next few weeks a tumor began to sprout out from the left hilus, and, shortly, subcutaneous nodules were discovered, which on biopsy were diagnosed as metastatic carcinomas. The pulmonary cancer grew rapidly, and the patient succumbed, with his left lung almost completely replaced by tumor.

Case 26.—In the second case [19] a woman of 57 was admitted to the hospital complaining of inability to walk, pain in the lumbar region radiating downward, and weakness of the right hand. The illness started with dull, persistent pain in the back,

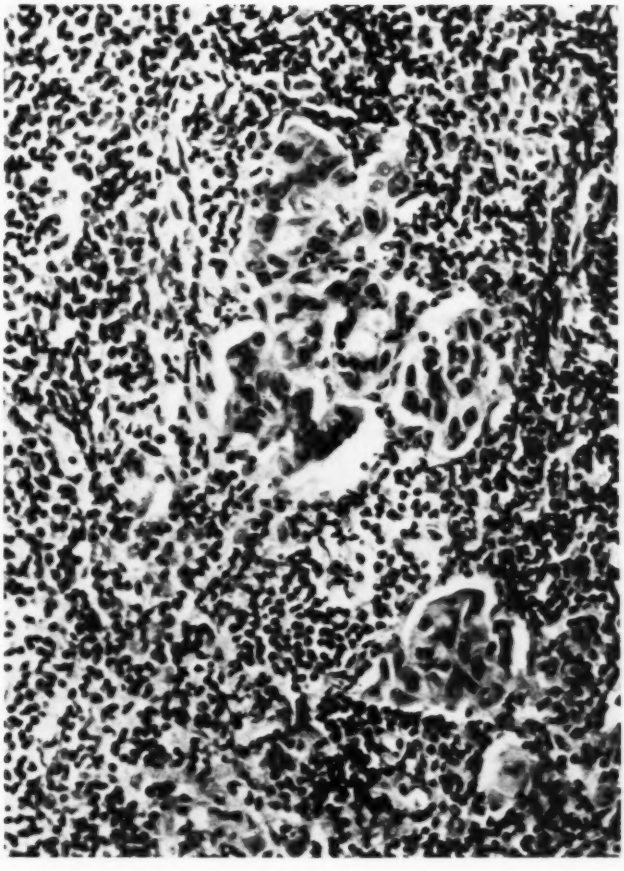


Fig. 7.—Metastatic inoculation of a giant-follicle lymphoblastoma by cancer cells from a bronchiogenic carcinoma.

extending to the gluteal region and the thigh, followed by difficulty in walking, night sweats, and small hemoptyses. An examination revealed tenderness in the lower left abdominal quadrant, several small nodules on the cervix, and an area of consolidation in the basal portion of the left lung. She was operated on for a myoma of the uterus. Following this she coughed up blood. Her lungs showed a scattered mottling, resembling the picture of miliary tuberculosis. She died 10 weeks after entry into the hospital. The autopsy showed a left bronchiogenic carcinoma with metastases to the lymph nodes, liver, adrenals, bones, and brain. One cerebral metastasis was found in the posterior parietal region, and another, within a meningioma about 2 cm. in size, located in the right frontal lobe (Fig. 8).

Greene and Strauss,[17] who observed cancer cells from one metastasis metastasizing to another metastasis, stated that cancerous tissue is a favorable soil for the growth of neoplastic cells from another cancer. It is, however, not understood whether one cancer serves as a point of "attraction" for tumor cells from another cancer or whether the phenomenon is merely a "freak of nature." This will not be understood until there is a final solution of the problem.

Summary

Twenty-four cases of primary multiple cancers, 20 double and 4 triple, were found at autopsy in 1514 cases of visceral cancer, an incidence of 1.54%.

The sum of available evidence indicates that in man cancer is solitary in about 98%

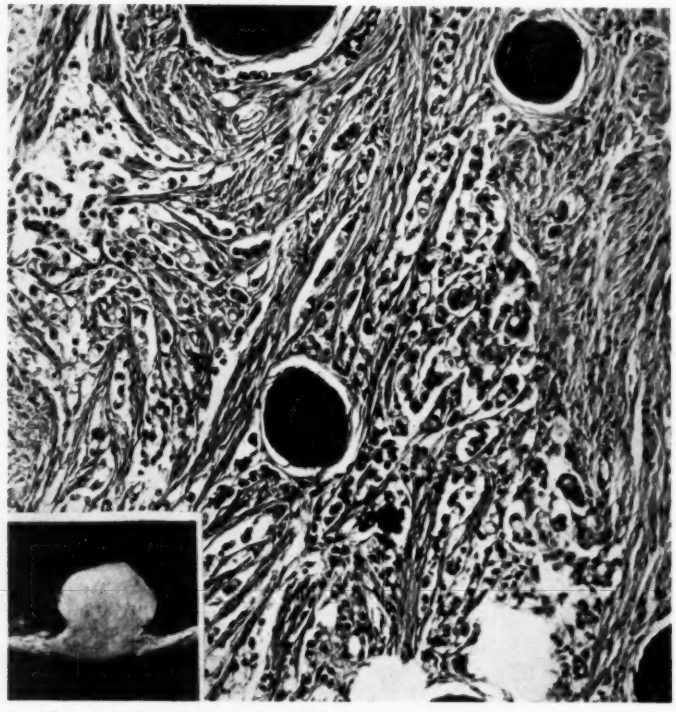


Fig. 8.—Metastatic inoculation of a meningioma by cancer cells from a bronchiogenic carcinoma. The cut surface of the meningioma is shown in the inset.

of cases. The solitariness, rather than the multiplicity, of human cancer is of compelling interest. The reason for the solitariness is not understood.

It is desirable to divide primary multiple cancers into two categories: (1) those which originate in organs of the same system, and (2) those which arise in organs of different systems. The multiplicity of cancers of the first category is very likely due to mere coincidence, while the advent of two or more cancers in the second category is due in all probability to a predisposition *sui generis*.

1560 Grand Concourse (57).

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Clinical Aspects of Primary Carcinoma of the Gallbladder

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About 3000 cases of primary carcinoma of the gallbladder have been reported since 1771, when Maximilian Stoll is said to have described the first case.[14] The marked interest in this disease has largely been the result of opportunities afforded in cancer prevention and in defining the etiology of an individual cancer.[8] Recently, attention has centered on more adequate surgical excision of the primary tumor and its regions of spread.

Incidence

Carcinoma of the gallbladder is found in 1% to 2% of operations on the biliary tract.[2,18] Nearly 10% of patients with symptomatic biliary tract disease who are 65 years of age or older will develop cancer of the gallbladder.[9] A practical estimated incidence is that gallbladder cancer will be encountered about three times each year on an active general surgical service.

Age and Sex

As with most types of cancer, gallbladder cancer occurs most commonly in the older age groups. About 90% of cases are found in persons 40 to 80 years old. Nearly 40% of cases are seen in patients who are in their sixth decade.[2]

The disease predominates in women. In most series, 70% to 80% of cases are found in women and 20% to 30% in men.[2,9]

Signs and Symptoms

The usual history of a patient with carcinoma of the gallbladder is indistinguishable from that of a patient with the benign complications of cholelithiasis. The patient is usually a woman past 50 who has had symptoms of gallbladder disease for more than 10 years. A few weeks or months prior to admission the patient has experienced an exacerbation of her symptoms, with moderately severe, constant right upper quadrant or epigastric pain. On examination, tenderness and a mass may be found in the right upper quadrant. Fever of low grade with occasional exacerbations is of frequent occurrence in the patients who harbor gallbladder cancer.

A history suggestive of chronic biliary tract disease of many years' duration is found in many reported series.[6,17] About 50% of patients give a history suggestive of chronic biliary disease for an average duration of 10 or more years. A sudden change in the character of the symptoms may indicate the presence of cancer. In other patients gallbladder cancer is present, but without symptoms. In such cases the lesion is usually an incidental finding in an asymptomatic gallbladder removed because it contained stones. About 6% of patients with cancer of the gallbladder have had gallbladder surgery prior to the development of their cancer.

Pain is the chief complaint in about 75% of cases. The pain is usually located in the right upper quadrant or epigastrium. It may be dull and constant or colicky and intermittent. Weight loss is present in over 60% of patients. Jaundice appears, and is of variable duration in about half the cases. The jaundice may be persistent and progressive, or intermittent and fluctuant. An enlarged liver or right upper quadrant mass

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From the Gastric Service of Memorial Center for Cancer and Allied Diseases.

is found in about 50% of the cases. The mass is frequently associated with some tenderness. Nausea, vomiting, ascites, and other symptoms of carcinomatosis may be present. Fistula formation and bowel obstruction sometimes occur and produce the symptomatology characteristic of these entities.[2,4,6,11,17]

It is evident that neither the signs nor the symptoms are characteristic exclusively of cancer of the gallbladder. A preoperative diagnosis of gallbladder cancer is made in about 20% of cases. However, this percentage is probably associated with a large number of false-positive diagnoses. There is nothing distinctive of gallbladder cancer, radiographically or in the various laboratory determinations which may be employed. Cytologic examination of aspirated duodenal contents has been of little diagnostic aid.[9]

Pathology

The gallbladder involved by primary cancer may appear enlarged, contracted, thickened, or normal externally. The wall may be thickened or thin and fibrous, with a gross appearance which is indistinguishable from that of cholecystitis, hydrops, or empyema of the gallbladder. In other cases, a solid tumor mass or projecting papillary growths occupy the gallbladder lumen. The nature of the lesion is all too commonly evidenced by infiltration and metastases. Multiple foci of origin of gallbladder cancer can sometimes be demonstrated in early lesions. The diffuse involvement by cancer of the mucosa of the gallbladder and extrahepatic bile ducts, seen in some cases, may be a result of the coalescence of multicentric foci of origin.[19] The extensive nature of most gallbladder cancers precludes determination of their site of origin. Any propensity which may exist for any particular area could be related to surface area.

Microscopically, over 90% of malignant tumors of the gallbladder are adenocarcinomas. Less than 10% are adenosquamous or squamous-cell carcinomas.[2]

Fig. 1.—Gross appearance of scirrhous adenocarcinoma of the gallbladder.

Rarely, carcinoid, leiomyosarcoma, and melanoma have been described as originating in the gallbladder.[1] A generally accepted classification of the adenocarcinomas is a division into the scirrhous, or infiltrative, form; the papillary, or villous, form, and the gelatinous, or mucoid, form. The scirrhous, or infiltrative, form (Fig. 1) constitutes about 70% of the adenocarcinomas. This type of adenocarcinoma is composed of a variable amount of fibrous connective tissue with interspersed epithelial cells. Usually, there is an extensive proliferation of cellular connective tissue with small amounts of atypical epithelial cells, which tend to form alveolar structures.

The papillary, or villous, form (Fig. 2) constitutes about 20% of adenocarcinomas. These lesions may arise on a polyp. In situ carcinoma arising on a polyp has been reported.[13] Papillary adenocarcinoma occasionally appears as a solitary pedunculated growth. Usually, the tumor grows toward the lumen of the gallbladder, producing a bulky mass, which has a minimal tendency to infiltrate locally. Spread along the bile ducts is common. These tumors tend to undergo necrosis and therefore predispose to infection of the gallbladder. The papillary growth is made of a central connective tissue stalk which is covered with cylindrical cells and infiltrated by atypical alveoli lined with cuboidal cells.

Fig. 2.—Gross appearance of a papillary adenocarcinoma of the gallbladder.

Mucoid, or gelatinous, carcinomas comprise about 8% of adenocarcinomas (Fig. 3). The tumor is friable, ulcerates easily, and may cause perforation of the gallbladder. The gallbladder wall and contiguous structures are widely infiltrated.

Squamous-cell carcinomas and the squamous-cell component of adenosquamous carcinomas probably arise from areas of squamous metaplasia, as demonstrated in experimental studies.[7] The squamous-cell component tends to be invasive and to metastasize early. The metastases from adenosquamous carcinomas may be squamous or adenocarcinoma in type, or may retain the same mixed microscopic features as the primary tumor.

Certain findings in experimentally induced gallbladder cancer seem pertinent to the interpretation of pathologic changes in gallbladder cancer in humans. As previously reported,[7] primary carcinoma of the gallbladder was induced in five of six cats that survived 23 to 32 months after the implantation of a single pellet of methylcholanthrene in the lumen of the gallbladder. The cancers were quite similar grossly, microscopically, and biologically to gallbladder cancer in the human. The cystic duct was ligated at the time of implantation of the methylcholanthrene pellet in four of the five cats that developed cancer. In these animals, tumor

Fig. 3.—Gross appearance of a mucoid adenocarcinoma of the gallbladder. The condition was treated initially as acute cholecystitis by cholecystostomy; right hepatic lobectomy subsequently performed (Patient S. D.).

growth was principally outward into adjacent structures. There appeared to be markedly increased intraluminal pressure and a distended gallbladder which had a fibrous wall containing cancer cells. The appearance was quite comparable to that of scirrhous, or infiltrative, adenocarcinomas in humans. A patent cystic duct was present in only one cat, but this seemed to permit growth of the tumor into the gallbladder lumen, with a resultant intraluminal tumor mass and minimal infiltration into adjacent structures. These findings suggest that the gross appearance and infiltrative capacities of cancer of the gallbladder in humans may be dependent on the patency of the cystic duct rather than on any ill-defined inherent growth potentiality of different types of cancer (Figs. 4, 5).

The spread of primary carcinoma of the gallbladder is by direct extension and by the lymphatic and vascular routes. The liver is involved by direct extension in 60% to 90% of cases. Obstructive biliary cirrhosis, ascending cholangitis, and multiple liver abscesses may develop secondarily to tumor growth. Other structures commonly and directly invaded by gallbladder cancer are the bile ducts, duodenum, stomach, colon, omentum, pancreas, portal vein, and abdominal wall. Metastasis usually occurs to the liver and to the regional lymph nodes. Perineural involvement or direct invasion of a nerve trunk is common. Generalized metastatic spread of gallbladder cancer occurs, but is infrequent. One of the commonest complications of gallbladder cancer is perforation into neighboring viscera or into the peritoneal cavity.

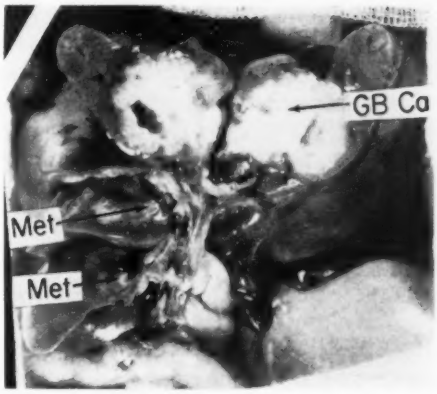

Fig. 5.—Primary adenocarcinoma of the cat's gallbladder induced by methylcholanthrene. The preparation is the same as that shown in Figure 4 except that the cystic duct was not ligated. Growth is predominantly intraluminal. Arrows labeled *Met* point to metastases to the liver; arrow labeled *GB Ca* points to the primary cancer.

From article by J. G. Fortner entitled Experimental Induction of Primary Carcinoma of the Gallbladder, published in *Cancer* (8:689-700, 1955), reproduced by permission of J. P. Lippincott Company, Philadelphia.

Fig. 4.—Primary adenocarcinoma of the gallbladder induced in the cat by methylcholanthrene. The cystic duct was ligated at the time of implantation of the carcinogen. Note that the cancer has grown predominantly outward into the liver rather than, as in Figure 5, into the gallbladder lumen.

From article by J. G. Fortner entitled Experimental Induction of Primary Carcinoma of the Gallbladder, published in *Cancer* (8:689-700, 1955), reproduced by permission of J. P. Lippincott Company, Philadelphia.

Treatment

Prophylactic.—Considerable interest has been manifested in the preventive aspects of gallbladder cancer. Since cancer of the gallbladder is associated with gallstones in 70% to 90% of cases, it would seem that this type of cancer could be prevented by cholecystectomy for both symptomatic and asymptomatic gallstones. Theoretically, about 90% of gallbladder cancer could be prevented by application of this principle. This would, however, entail cholecystography on all patients of certain age groups and a

cholecystectomy on possibly 15% or 20% of the general population aged 40 and over. This is obviously impractical. There is general agreement that symptomatic gallstones or gallstones incidentally found at laparotomy should be treated by cholecystectomy. The controversial issue actually arises in defining the treatment of asymptomatic gallstones found incidentally during a diagnostic work-up. A practical compromise would seem to be that gallstones in a normally functioning gallbladder can be observed and that gallstones in a poorly functioning or nonfunctioning gallbladder should be treated by cholecystectomy, for cancer rarely, if ever, develops in a normal gallbladder. Benign complications will eventually develop in some of the patients with cholelithiasis who are observed. However, the great percentage of gallstones which have caused no symptoms in persons followed clinically or examined at necropsy, the occasional death or serious complication which follows routine cholecystectomy, and the present-day low mortality following cholecystectomy for inflammatory lesions of the gallbladder make the observation of patients with asymptomatic gallstones in a normally functioning gallbladder an acceptable risk.

Surgical.—There is little hope at the present time for cure of about 75% of patients with primary carcinoma of the gallbladder because their disease is too advanced when first diagnosed. In nearly 25% of cases it appears limited to the gallbladder region and may be surgically curable. As yet, this potential is unrealized. Therapy in the form of cholecystectomy has been associated with a 2%-3% five-year survival rate.[2,3] Cholecystectomy with excision of the gallbladder bed and regional lymph node dissection has been tried but has failed to improve the curability rate.[9]

We know of only two patients with primary carcinoma of the gallbladder treated on the gastric service at Memorial Center who have survived five or more years. One (R. D.), previously reported by Booher and Pack,[3] had had a cholecystectomy with removal of regional lymph nodes on Aug. 1, 1941. Pathologic examination revealed a primary adenocarcinoma, Grade 3, of the gallbladder with lymph node metastases. On July 21, 1952, nearly 11 years later, this patient was found to have an extensive carcinoma involving the stomach. An extended total gastrectomy was performed. Histologic examination failed to ascertain definitely whether the cancer arose primarily in the stomach or was metastatic adenocarcinoma from the gallbladder cancer. The patient died of carcinomatosis on March 1, 1953, or 11 years 7 months after initial treatment.

The second patient (M. G.) from the Memorial Center, previously reported by

Fig. 6.—Typical appearance of a right hepatic lobectomy specimen.

Cases of Primary Carcinoma of the

Patient	Sex	Age	Duration of Symptoms	Surgery Prior to Lobectomy	Operative Findings
L. M.*	F	61	6 wk.	Laparotomy & biopsy	Small firm multinodular gallbladder; multiple areas of metastatic tumor in r. lobe; normal l. lobe; multiple enlarged nodes in gastrohepatic ligament
K. E.*	F	53	20+ yr.	Cholecystectomy, June, 1953; radio-active cobalt bomb therapy for local recurrence Feb., 1954	Recurrent ca. in cholecystectomy wound; 2 cm. tumor mass in l. lobe contiguous with falciform ligament; recurrent ca. in gallbladder bed with adherence of duodenum
J. G.*	M	65	3 mo.	None	Gallbladder largely replaced by tumor with direct invasion and metastases to r. lobe of liver; metastases to lymph nodes of hepatic pedicle & retroduodenal area
S. D.	F	69	3 mo.	Cholecystostomy	8×10 cm., thick-walled gallbladder; no liver metastases; large nodes in retroduodenal & celiac areas
L. L.†	F	53	6 mo.	Cholecystectomy 3 days prior to lobectomy	No tumor in liver or elsewhere discernible
T. L.	F	68	2-3 mo.	None	Gallbladder replaced by tumor invasion of & metastases to r. lobe of liver
I. H.	F	56	"Many years"	Exploratory laparotomy 10 days previously	Gallbladder replaced by tumor with direct invasion into r. lobe; adherence of tumor to duodenum & r. transverse colon; enlarged regional lymph nodes

* Previously reported.[1]
† Previously reported.[5]

Tabah and McNeer,[16] had had a cholecystectomy for multiple adenomatous polyps with in situ carcinoma of the gallbladder at the age of 40. She has now survived over seven years and has no demonstrable evidence of recurrent or metastatic cancer. This patient is of particular interest, for she is one of a large family which is being studied to determine whether gallbladder polyps are familial. One sister (A. H.) of this patient (age 41) was found to have small, constant, lucent filling defects in the gallbladder on the cholecystogram. Cholecystectomy was performed. Pathologic examination of the gallbladder by Dr. A. C. Allen revealed "minute papillomas with hyperplastic mucosa." Several younger members of this family were studied, but no abnormality of the gallbladder was found.

The survival for five years of a patient with gallbladder cancer currently constitutes a medical curiosity. The poor results obtained by cholecystectomy, with or without excision of the gallbladder bed and regional lymph node dissection, are a sound basis for more aggressive surgical therapy. Anatomical and pathologic considerations indicate that the actual and potential area of spread of gallbladder cancer can most adequately be removed by total right hepatic lobectomy and regional lymph node dissection (Fig. 6).

Gallbladder Treated by Right Hepatic Lobectomy

Operation	Pathology	Postoperative Complications	Survival	Cause of Death
10/26/53 R. hepatic lobectomy & regional lymph node dissection	Adenocarcinoma of the gallbladder, Grade 3, with liver & lymph node metastases	1. Recurrent & persistent r. pleural effusion 2. Peripheral edema of undetermined etiology	4½ mo.	Carcinomatosis
8/23/54 R. hepatic lobectomy with resection of tumor, nodule in l. lobe & portion of duodenum, colon, abdominal wall, 5/25/56: resection local recurrence of tumor greater curvature stomach & r. costal arch	Primary adenocarcinoma of gallbladder with metastases	Wound infection	2 yr., 1 mo.	Unknown; presumed carcinomatosis
2/12/54 R. hepatic lobectomy & regional lymph node dissection	Papillary adenocarcinoma of gallbladder with liver & lymph lymph node metastases	Gastric dilatation; ileus; uremia; oliguria	7 days	Postoperative complications
3/11/55 R. hepatic lobectomy & regional lymph node dissection	Primary adenocarcinoma, Grade 3, of gallbladder extending entirely through gallbladder wall to become nearly contiguous with hepatic cells; metastatic adenocarcinoma to multiple lymph nodes	Bronchopneumonia	6 days	Postoperative complications
3/28/55 R. hepatic lobectomy & regional lymph node dissection	Infiltrating, partly papillary adenocarcinoma of gallbladder; regional lymph nodes & liver negative for tumor	None	3+ yr.	Alive, N. E. D.
5/30/56 R. hepatic lobectomy & regional lymph node dissection	Adenocarcinoma of gallbladder, Grade 3, invading liver	Gastrointestinal hemorrhage; intestinal fistula; septic thrombophlebitis; uremia; anasarca; liver failure	7 days	Postoperative complications
10/16/57 R. hepatic lobectomy, resection wedge of duodenum & colon; regional lymph node dissection	Adenocarcinoma, biliary tract type involving duodenum & metastatic to liver & supraduodenal lymph nodes	Duodenal & colon fistula with generalized peritonitis, septicemia, pleural effusion, pulmonary congestion, peripheral edema	13 days	Postoperative complications

This concept has been applied since October, 1953, by members of the gastric service of Memorial Center. The surgically incurable state which is initially manifested by about three of four cases of this relatively infrequent cancer imposes severe limitations on evaluating hepatic lobectomy as a method of treatment. Our experience to date is as follows: Since October, 1953, seven patients with primary carcinoma of the gallbladder have been subjected to total right hepatic lobectomy and regional lymph node dissection (Table). The initial results in four of these cases have previously been reported.[5,13] At the present time, one patient (L. L.), a case of Dr. Richard Brasfield's is living and well without evidence of cancer, three years after hepatic lobectomy. One patient (K. E.) survived two years and one month. However, reoperation was necessary for removal of two foci of local recurrence, one year nine months after lobectomy. She died four months later, presumably of her cancer. A third patient (L. M.) died of carcinomatosis four and one-third months after lobectomy. Four of the patients died of complications 6 to 13 days after lobectomy. The operative mortality for these cases is thus 57%.

In a critical analysis of these seven cancers of the gallbladder, and with due appreciation of the stages and extent of the disease as we encountered it, it is only fair to state that for six of the seven patients the operation was one of desperation. Five of the seven patients had experienced previous laparotomies for their cancers. In four of these seven patients proved metas-

tases to regional lymph nodes were found and removed. We have made it a practice routinely to dissect the lymph node drainage basin of the gallbladder from the portal fissure down the hepatoduodenal ligament to include the supra- and retroduodenal lymph nodes, which we have often found to be involved by metastatic gallbladder cancer.

It is evident that the number of cases of gallbladder cancer treated by right hepatic lobectomy and regional node dissection is too small to permit evaluation of the procedure as yet. All but one of the patients treated to date have had extensive but localized cancer. The one exception is alive and well. We believe that right hepatic lobectomy with regional node dissection is indicated for those gallbladder cancers which are confined to a surgically resectable location.

Conclusions and Summary

The natural history of primary carcinoma of the gallbladder has been well documented by the numerous studies, in which about 3000 cases have been reported. A summary of the findings immediately pertinent to the understanding and care of the patient with gallbladder cancer seems warranted.

This disease predominates in women in their sixth decade of life. About three cases will be encountered each year on an active general surgical service. The usual history of patients with cancer of the gallbladder is indistinguishable from that of a patient with the benign complications of cholelithiasis. Nothing distinctive of gallbladder cancer is found radiographically or in the various laboratory tests which can be performed. Diagnosis rests upon the findings of abdominal exploration at the time of surgery or of necropsy.

Ninety per cent of malignant tumors of the gallbladder are adenocarcinomas. Silent, early, and diffuse spread, both by direct extension and by metastasis, is characteristic of these tumors. A surgically incurable lesion thus evolves in about three of four cases by the time of diagnosis. Cholecystectomy with or without excision of the gallbladder bed and regional node dissection has resulted in only an occasional five-year survival. More extensive surgery in the form of right hepatic lobectomy and regional node dissection is therefore warranted. The infrequency of cancer localized to the gallbladder region permits only a slow accumulation of experience. Seven patients with primary cancer of the gallbladder have been treated by right hepatic lobectomy and regional node dissection by members of the gastric service at Memorial Center. One patient has survived over three years and is alive and well. One patient survived two years and one month before succumbing. Another patient survived four and one-third months before dying of cancer. Four patients died in the immediate postoperative period, giving an operative mortality rate for these cases of 57%. Only two patients with primary cancer of the gallbladder who have been treated on the gastric service of Memorial Center are known to have survived five or more years after diagnosis. Interesting features of these two cases are presented.

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Carcinoma of the Prostate

A New System of Classification

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In 1925 Broders [1] presented a method whereby the degree of malignancy of a tumor could be assessed, recorded, and communicated readily to the clinician. Realizing that the percentage of undifferentiated cells determines the malignant potential, he based his system on the ratio of these to the differentiated cells as follows:

	Differentiated Cells	Undifferentiated Cells
Grade 1	100%-75%	0%- 25%
Grade 2	75%-50%	25%- 50%
Grade 3	50%-25%	50%- 75%
Grade 4	25%- 0%	75%-100%

Grade 1 here, then, represents the least malignant tumors, whereas Grade 4 represents the most malignant tumors.

He graded and followed 880 epitheliomas, finding a very close correlation between the tumor grade and the therapeutic result.

Subsequently, this excellent system has been applied to carcinoma of the prostate. Here, too, the grade and prognosis are related and vary proportionately. Table 1 shows the percentage of patients with metastases in Kahler's [4] cases and the survival figures for Thompson's [7] and Pool and Thompson's [6] series. The increase in metastases and the worsening of prognosis with the increase in grade are apparent.

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TABLE 1.—*Percentage of Metastases, Survival, and Grade of Malignancy in Three Series*

	No. of Cases	1	2	3	4
Kahler	189				
Patient with metastasis		33	50	84	100
Thompson	881				
5-yr. survival figures		60.9	22.5	7.7	0.0
Pool	1534				
3-yr. survival figures		72.3	52.2	37.7	17.9
5-yr. survival figures		59.5	34.1	16.2	5.6
10-yr. survival figures		40.0	9.4	3.1	0.0

Although obviously a dependable source of information, this system has not gained wide acceptance. This is to be regretted, for when such a system is used, a means of transfer of more exact information between the clinician and the pathologist is possible.

Another method of classification, based on more readily apparent characteristics, seems necessary. It became evident to us that the more malignant tumor not only shows less differentiation but also changes in histological pattern. This pattern, then, might form a more acceptable basis for classifying these lesions.

Present Classification

The following system, based on the degree of cytologic atypism and anaplasia, has been worked out. It is arbitrarily divided into four categories, each of which is termed a "class," to distinguish it from Broders'. The most malignant area is used to classify each tumor, as we feel that this determines its course.

Class I (Fig. 1).—Cases showing the least evidence of aggression and capacity for growth are included. The cells are morphologically uniform. In nearly every case, the individual cell is small and contains moderately abundant, faintly granular cytoplasm. The nuclei are proportionate and not unduly hyperchromatic. Chromatin is fairly coarse, and the nucleoli are small but conspicuous. The cells are arranged in regular glandular pattern around small alveolar

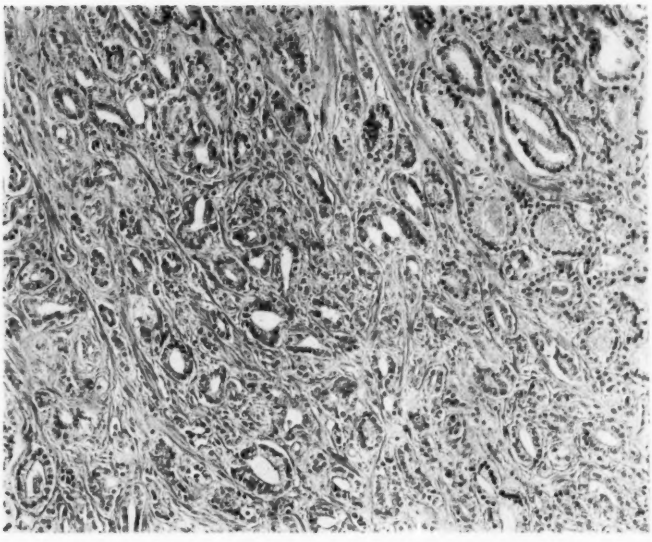

Fig. 1.—Carcinoma of the prostate, Class I.

spaces. Orientation of the cells is well maintained, and some of the lumina contain fluocculent precipitate. There is evidence of invasion of the surrounding tissues, with penetration of the stroma between the true prostatic ducts. This feature is not extensive and often isolates normal structures. Mitotic figures are not common.

Class II (Fig. 2).—These tumors are regarded as slightly more malignant. The neoplastic cells are again disposed in glandular pattern, but the arrangement is less regular and less uniform. In general, the glandular structures are larger and the luminal spaces are irregular and imperfect. In some tumors the epithelial cells are arranged in large sheets with narrow fenestrations. The individual cells are less well oriented. The luminal content is scanty or absent. Usually the cells are larger than

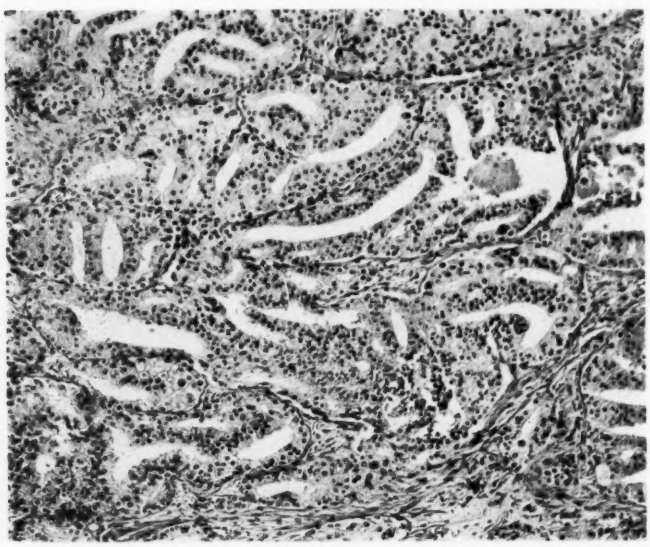

Fig. 2.—Carcinoma of the prostate, Class II.

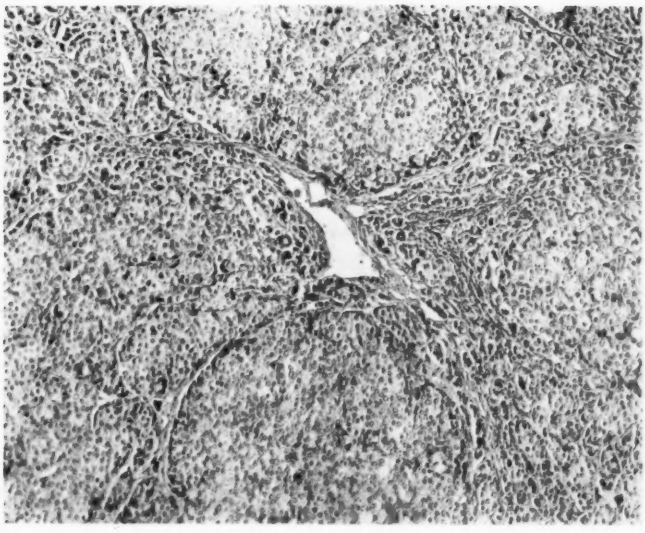

Fig. 3.—Carcinoma of the prostate, Class III.

normal. The ratio of the size of the nucleus to the amount of cytoplasm is increased. Hyperchromatism is more prominent, as is nuclear irregularity. Mytotic figures are more numerous than in Class I tumors, but are not abundant. Invasion into surrounding glandular tissue and extension into the capsular structures are more evident.

Class III (Fig. 3).—These tumors usually show an increase in epithelial cellularity over those of Class II. The cells usually occur in large, irregular sheets, which are interrupted by narrow and poorly defined lumina. At times a tendency toward a papillary disposition is apparent. The individual tumor cell is large and shows marked variation in size. Cytoplasm is relatively scanty and granular. The nuclei are disproportionately large and hyperchromatic. Nucleoli are much larger and are deeply basophilic. In many

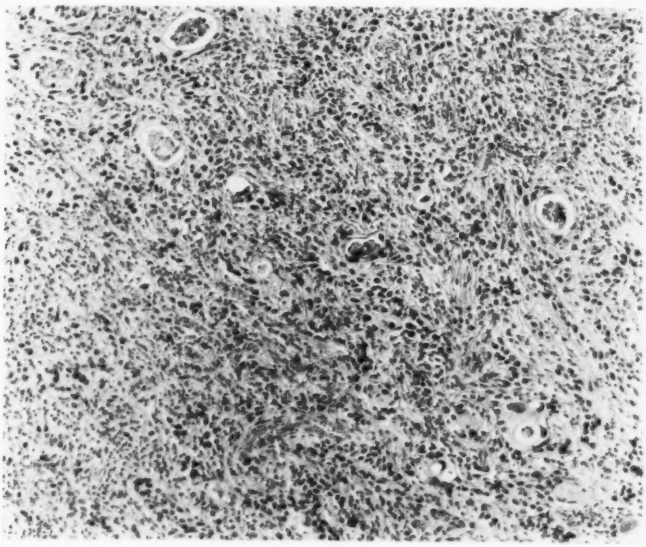

Fig. 4.—Carcinoma of the prostate, Class IV.

areas the nuclei have a vesicular appearance, which tends to accentuate their prominence. Mitotic figures are more numerous than in Class II. Invasion of surrounding structures is evident, and adjacent tissues are atrophied.

Class IV (Fig. 4).—These tumors are regarded as most malignant. In these tumors the cells are seldom arranged in a recognizable glandular pattern; oftener they are in solid sheets and cords. In some cases these cords are very narrow and appear to ramify through the prostatic stroma almost in single file. The tumor cells are very large and contain moderately abundant, granular cytoplasm. The nuclei are disproportionately large and often gigantic. Hyperchromatism is marked, and acidophilic nuclei are often present. Mitotic figures are numerous, and multinucleated tumor cells are not infrequent. In addition to direct invasion of surrounding prostatic tissue, these tumors show increased tendency to permeate lymphatic spaces and to grow into preexisting prostatic ducts. (This classification was worked out by S. H. Auhbach.)

Observations

Variations in composition of individual tumors were observed, of course. This was seldom seen in well-differentiated tumors but was notable in more rapidly advancing neoplasms. It also appeared that the growth of some tumor cells became accelerated with the passage of time. This impression was gained from the several cases in which repeated resections were performed for purposes of palliation.

Permeation of the perineural lymphatic channels of the capsule did not appear to be of the serious prognostic import that was expected. This finding is a valuable diagnostic criterion, but is less important from a prognostic standpoint. The influence of castration and hormone therapy do not pertain to the above descriptions.

Eighty-three cases were available for study, and these were reviewed and graded. The reviewer (S. H. A.) had no knowledge of the patients or the clinical course which they followed. Of these cases, 37 fulfilled the criteria for radical surgery and were so treated. Table 2 shows the percentage of cases which fall into each class. These percentages closely approximate those noted by Kahler,[4] Thompson,[7] Pool,[6] and Greene.[3] All of Greene's [3] cases were of "occult carcinoma" and were not diagnosed previous to operation.

All cases in which on rectal examination carcinoma of the prostate is suspected are given the following work-up: a complete blood count; urinalysis; urine culture; nonprotein nitrogen determination; intravenous pyelography; chest, lumbar spine, and pelvis films; acid and alkaline phosphatase determinations, cystoscopy, and other tests when history and physical examination dictate. We find the x-ray a more dependable indication of the presence of metastases than the acid phosphatase level. After the work-up, if no evidence of metastasis is found, a perineal biopsy is performed. Frozen sections have proved to be unreliable in our hands; so we wait for the reading of the permanent slides before proceeding with definitive procedure. If carcinoma is present, the perineal technique of Young [8] or the retropubic technique of Millin [5] is then executed to carry out the radical prostatectomy.

TABLE 2.—*Distribution by Grade: Comparison of Broders-Auerbach Systems*

	No. of Cases in Series	Classes				Types of Treatment Included
		I	II	III	IV	
Kahler	195	19.0	50.0	27.5	3.5	All types
Thompson	881	12.7	31.4	35.5	20.4	All types
Auerbach	83	32.6	42.0	23.0	2.4	All types
Greene	83	85.6	13.2	1.2	0.0	Found incidentally at time of T. U. R.
Auerbach	37	51.0	38.0	11.0	0.0	Suitable for radical procedure

TABLE 3.—*Summary of Cases by Auerbach's Classification*

		Class I		Class II		Class III		Class IV	
		No.	%	No.	%	No.	%	No.	%
Metastasis	Admission	0	0	6	17	7	37	1	50
	Later	0	0	9	26	9	47	1	50
Extension	Admission	3	11	6	17	5	26	1	50
	Later	1	4	5	14	2	11	1	50
	With met/ext. *	1	4	7	20	2	11	0	0
Living	Without met/ext.	20	74	15	42	1	5	0	0
	Follow-up, avg. yr.	3.14		3.17		2.83		0	0
	Lost to follow-up, avg. yr.	1		1		1			
	With met/ext.	0	0	8	20	12	47	2	100
Dead	Without met/ext.	5	14	4	9	3	16	0	0
	Survival, Avg. yr.	3		2.78		1.9		0.3	
	Total (83)	27	32.6	35	42	19	23	2	2.4

* Metastasis or extension.

We find that this delayed procedure is not a handicap and that it is made easier by the first, as a line of cleavage is established between the prostate and the rectum. The radical procedure is therefore done from 7 to 10 days after the biopsy. Those cases not suitable for radical surgery, which do not show roentgenological evidence of metastases, are treated by colloidal gold injection, orchiectomy, and estrogens. Those with demonstrable metastases are treated only by orchiectomy and estrogenic therapy. We have found chlorotrianisene (TACE) to be the most satisfactory of the available agents. The breakdown of all of our cases according to our pathological classification is presented in Table 3.

A definite trend is noted, starting with Class I, in which none of the cases showed extension or metastases and 74% are alive without recurrence after an average of three years, and ending with Class IV, in which both patients had advanced tumor on admission and both were dead within three months. These two patients, incidentally, had had symptoms of prostatism for only three months prior to the time of admission.

Table 4 lists those cases not suitable for radical procedure because they failed to fulfill one or more of the criteria for this operation (Colston [2]). Again, the general worsening of the patient's state appears as the classification number increases. Note that the percentage of cases in Class I has now fallen from the 32.6%, obtained in Table 3, to 17% and the percentage in Class II has risen from 42% to 46%.

Table 5, listing only those cases suitable for radical prostatectomy, shows the dramatic increase in percentage of patients in

TABLE 4.—*Summary of Cases Treated Conservatively According to Auerbach's Classification*

		Class I		Class II		Class III		Class IV	
		No.	%	No.	%	No.	%	No.	%
Metastasis	Admission	0		6	20	7	46	1	50
	Later	0		9	43	9	62	1	50
Extension	Admission	1	12	5	25	4	27	1	50
	Later	1	12	5	25	1	6	1	50
	With met/ext.	1	12	7	33	1	6	0	
Living	Without met/ext.	1	50	1	5	0	0	0	
	Follow-up, avg. yr.	4.1	..	3.3	..	1	..	..	..
	Lost to follow-up, avg. yr.	1	..	1	..	1	..		
	With met/ext.	0		8	33	12	62	100	2
Dead	Without met/ext.	2	12	4	14	1	6	0	
	Survival, avg. yr.	1		2.8	..	2	..	0.3	..
	Total (46)	8	17	21	46	15	33	2	4

TABLE 5.—*Radical Prostatectomy Series*

		Class I		Class II		Class III		Class IV	
		No.	%	No.	%	No.	%	No.	%
Metastasis	Admission	0	0	0	0	0	0	0	0
	Later	0	0	0	0	0	0	0	0
Extension	Admission	2	4	1	3	1	25		
	Later	0	0	0	0	1	25		
Living	With met/ext.	0	0	0	0	1	25		
	Without met/ext.	16	84	14	100	1	25		
	Follow-up, avg. yr.	2.9	..	3.1	..	3.75	..		
Dead	With met/ext.	0	0	0	0	1	25		
	Without met/ext.	3	16	0	0	1	25		
	Survival, avg. yr.	0.1	..	..	..	1.5	..		
	Total	19	51	14	38	4	11		

the least malignant class (Class I) and the total absence in Class IV.

Summary and Conclusions

In each division of our series the prognosis worsened as the grade increased. Cases suitable for radical prostatectomy show a high percentage of Class I lesions. All of these cases had small, presumably early lesions. Conversely, cases not suitable for radical surgery show a low percentage of Class I lesions.

Broders' classification has proved to be useful but has not gained wide acceptance.

Auerbach's system, based on the histological pattern, appears to have the same connotation and in our opinion can be quickly assimilated by both pathologist and clinician.

The use of this classification gives the surgeon additional exact information which, when weighed with the other pertinent factors, is useful in the selection of a therapeutic regimen for the individual case.

A convenient and standard medium for the estimation of malignant potential is thus established.

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Results of Surgery for Thyroid Cancer

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The surgery to be applied for cancer of the thyroid continues to be controversial. Because of the multiplicity of characteristics and the unlimited predictability of this disease, the short-term surgical follow-up studies usually reported have been found difficult to appraise. Long follow-up observations would, if available, bring in the many variables of life. It is, of course, extremely important to determine now, if possible, and from existing data whether the proper surgical therapy is being applied.

This paper presents the cases of thyroid cancer seen for their pathological diagnosis and surgical treatment at The Johns Hopkins Hospital from 1930 to 1956. In an attempt to evaluate the effect of the surgical treatment on the course of the cancer, the pathogenesis of recurrences and cancer death have been related to the extent of the original surgery.

Material and Observations

One hundred thirty-nine cases of cancer of the thyroid were primarily diagnosed and treated at The Johns Hopkins Hospital in the 26-year study period. Additional patients, with diagnosis and initial treatment elsewhere, were seen for further therapy. The latter group will not be discussed in detail here. It is noteworthy that the number of cases of thyroid cancer seen primarily at this hospital increased from 10 to 49 between the first and the last five-year period.

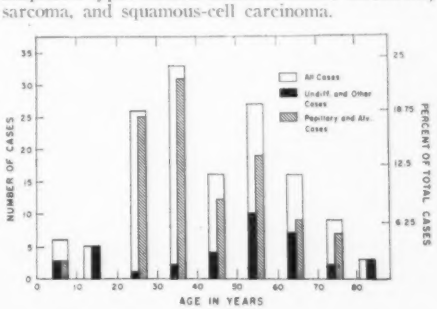
The original tissue sections were reviewed for all cases with the given diagnosis of thyroid cancer. When this diagnosis could not be confirmed, the cases were excluded. The pathological division, a slight modification of that of Warren and Meissner,[7] is listed in Table 1.

TABLE 1.—*Pathological Classification of Thyroid Cancer*

	No.	%
Papillary adenocarcinoma	70	50.3
Alveolar adenocarcinoma	40	28.8
Hürthle-cell carcinoma	3	
Undifferentiated carcinoma	25	18.0
Giant-cell carcinoma	6	
Small-cell carcinoma	3	
Sarcoma	3	2.2
Squamous-cell carcinoma	1	0.7
Total	139	100.0

Female patients outnumbered male patients 3:1. This ratio was found to be greatest for the papillary and alveolar adenocarcinoma groups. The incidence for these groups was greatest in the third and fourth decades but the frequency continued to be high through the sixth decade (Fig. 1). For the undifferentiated and other more anaplastic cancers the greatest incidence occurred in the sixth and seventh decades.

Fig. 1.—Occurrence of thyroid cancer in the different age groups. A breakdown is made into the less and the more malignant pathological classifications. Undifferentiated and other more anaplastic types include undifferentiated carcinoma, sarcoma, and squamous-cell carcinoma.



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Presented before the Society of Head and Neck Surgeons, Baltimore, April, 1958.

† Dr. Ward died Feb. 16, 1958.

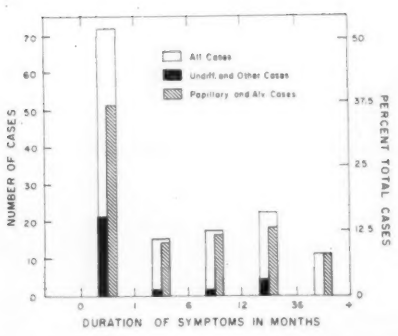

Fig. 2.—Duration of symptoms before histologic diagnosis was made.

Over 50% of the patients had had symptoms referable to the neck, or specifically to the thyroid, such as a cervical mass or goiter, for less than one month before the tissue diagnosis was made (Fig. 2). The symptomatic period extended from the discovery of an unknown thyroid nodule on routine physical examination to the presence of a goiter for over 50 years.

In Figure 3 are shown the thyroid findings on the initial examination. It is to be noted that 42% of these malignant tumors were found in a single palpable mass or nodule. It can be seen that if a single nodule was palpated on physical examination, the likelihood that the tumor was one of the less malignant types of thyroid cancer was 7:1. If nodules were multiple, the cancer was only two and one-half times as likely to be of the less malignant type, and if there was a diffuse enlargement of the gland, it was one and seven-tenths times as likely to be of low malignancy. In this series when cervical nodes alone were the only evidence of disease, all tumors were of the papillary or alveolar adenocarcinoma histologic type.

Eight patients (5.7%) were found to be hyperthyroid, as indicated by increased basal metabolic rate, protein-bound iodine, or radioactive-iodine uptake. In five patients the thyroid cancer was associated with papillary or alveolar adenocarcinoma. The total incidence differs significantly from the earlier-reported 26% of Ward et al.,[8] owing to the present rejection of cases presenting only clinical symptoms of hyperthyroidism.

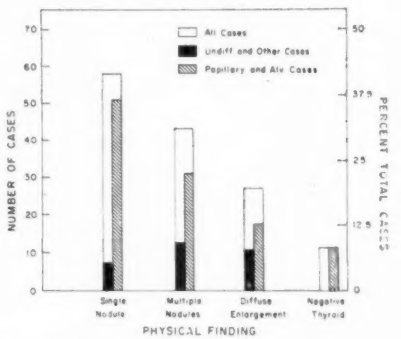

Fig. 3.—Physical state of the thyroid gland at examination at the time of histologic diagnosis of thyroid cancer. Note the comparison of occurrence of the less and the more malignant pathological classifications for each physical finding (see text).

TABLE 2.—*Surgical Procedures*

Pathology	No. Cases	Operations				
		Biopsy	Partial Thyroidectomy	Total Thyroidectomy	Radical Neck Dissection	Excision Palpable Nodes
Papillary adenocarcinoma	70					
Single operation only	58	2	50	4	10	12
Multiple operations	12	1	13	2	4	12
Alveolar adenocarcinoma	40					
Single operation only	33	2	25	6	3	4*
Multiple operations	7	1	10	1	1	3*
Undifferentiated carcinoma	25	9	13	3	2	--
Sarcoma	3	1	1	1	--	--
Squamous-cell carcinoma	1	--	1	--	1	--

* Includes one median sternotomy for excision of mediastinal nodes.

In Table 2 are shown the type and number of times each surgical procedure was performed. Biopsy consisted of removal of tissue for diagnosis only in association with a nonresectable lesion. Partial thyroidectomy consisted of removal of any amount of the gland, including the tumor but leaving some known thyroid tissue. Total thyroidectomy removed all thyroid tissue in the anterior neck. The radical neck dissections consisted of excision of the entire sternocleidomastoid muscle and the internal jugular vein, together with all lymph nodes from the clavicle to the base of the skull. Excision of only the palpable nodes included the removal of the individual lymph nodes palpable in the neck at the time of thyroid exploration. A combination of these procedures was frequently performed. It is to be noted that 17% of the patients with papillary adenocarcinoma and 17% of those with alveolar adenocarcinoma required multiple procedures to combat recurrences. One patient was subjected to four such operations in an attempt permanently to eradicate his cervical disease. The original surgery in the majority of cases consisted, as is seen, of partial removal of the thyroid gland.

TABLE 3.—*Five-Year Survival*

	Absolute		Determinate	
	No.	%	No.	%
Papillary adenocarcinoma	(31/44)	70.5	(31/39)	79.5
Alveolar adenocarcinoma	(13/29)	45.0	(13/22)	59.0
Undifferentiated carcinoma, sarcoma, squamous-cell carcinoma	(6/21)	28.6	(6/21)	28.6
Over-all	(50/94)	53.2	(50/81)	61.7

Prophylactic neck dissections were not usually performed. The incidence of metastases to local cervical nodes in this series could, therefore, not be accurately determined. Only 13 radical neck dissections, all unilateral, were primarily performed for papillary or alveolar adenocarcinoma. All of the seven patients with clinically suspicious lymph nodes and two without had node metastases.

TABLE 4.—*Ten-Year Survival*

	Absolute		Determinate	
	No.	%	No.	%
Papillary adenocarcinoma	(11/21)	52.4	(11/15)	73.3
Alveolar adenocarcinoma	(7/19)	36.8	(7/13)	53.8
Undifferentiated carcinoma, sarcoma, squamous-cell carcinoma	(4/12)	33.3	(4/12)	33.3
Over-all	(22/52)	42.3	(22/40)	55.0

Determinate survivals without evidence of disease of 79.5% for papillary adenocarcinoma and 59% for alveolar adenocarcinoma were found at the end of five years (Table 3). At 10 years the values were 73.3% and 53.8%, respectively (Table 4). The values for undifferentiated carcinoma, sarcoma, and squamous-cell carcinoma were 28.6% at 5 years and 33.3% at 10 years. The higher survival rate at 10 years occurred because the time since operation had been too short to include all deaths seen in the five-year follow-up period. The determinate five-year survival in all cases of all pathological types seen for their primary diagnosis and treatment regardless of operability was 61.7% at 5 years and 55% at 10 years.

A tabulation of deaths from all causes is given in Table 5. In 10 of the 13 deaths in the patients with papillary adenocarcinoma, in 6 of the 8 deaths in patients with alveolar adenocarcinoma, in 11 of the 14 deaths in patients with undifferentiated carcinoma, and in both the deaths in the pa-

TABLE 5.—*Over-All Tabulation of Deaths*

Pathology	Total Deaths		Average Survival, Yr.	Median Survival, Yr.	Range Survival, Yr.
	No.	%			
Papillary adenocarcinoma	13	18.5	4.6	4.0	0-23
Alveolar adenocarcinoma	8	20.0	5.6	4.5	3-13
Undifferentiated carcinoma	14	56.0	1.5	0.3	0-7
Sarcoma	2	66.0	0.2	0.2	0-0.4
Squamous-cell carcinoma	0	—	—	—	—

TABLE 6.—*Distant Metastases in Thyroid Cancer*

Pathology	Cases, No.	Cases with Metastases		Location		
		No.	%	Bone	Lung	Other
Papillary adenocarcinoma	70	7	10	2	6	1 *
Early		5		2	4	1
Late		2		0	2	0
Alveolar adenocarcinoma	40	10	25	6	5	3 †‡
Early		5		2	2	2 ‡
Late		5		4	3	1 *
Undifferentiated carcinoma	25	12	48	4	4	6 ‡
Sarcoma	3	0				
Squamous-cell carcinoma	1	0				

* Skin.
† Pancreas.
‡ Mediastinum.

tients with sarcoma of the thyroid cancer was still present.

The sites of distant metastases for the various pathological classifications, as determined by clinical examination or necropsy, are shown in Table 6. The late metastases will undoubtedly show an increase with a longer follow-up period.

In 8 of the 139 cases (5%) another form of cancer preceded, was associated with, or followed the thyroid disease. Five of these cancers occurred in patients with papillary adenocarcinoma, one in a patient with alveolar adenocarcinoma, and two in patients with undifferentiated carcinoma. These cancers were parotid carcinoma, embryonal carcinoma of the testis, mixed tumor of the lacrimal duct, carcinoma of the uterus, squamous-cell carcinoma of the lower lip, and squamous-cell carcinoma of unknown origin invading the trachea and thyroid, one case each, and carcinoma of the breast, two cases.

Comment

The statistics of this series are in general agreement with most published data on thyroid cancer.[1,2,4,5,7] The five- and even the ten-year survival figures for thyroid cancer of the papillary and alveolar histologic types have been found to be misleading because of the duration of the natural history of this disease. It was necessary, therefore, to evaluate the surgical treatment by other means. This has been done by an analysis of the pathogenesis of recurrences and of death when such occurred in patients with initially resectable cancers. Such study has directed the way for altering the primary surgery.

In Table 7 are listed the recurrences in patients with initially resectable lesions. The Table includes all patients in this category regardless of length of follow-up observations. The recurrence rate of papillary adenocarcinoma was 27.4% in a group of

TABLE 7.—*Recurrences in Thyroid Cancer*

Pathology	Total Cases, No.	Resectable Cases, No.	Recurrences		Location		
			No.	%	Thyroid	Cervical Nodes	Distance Metastases
Papillary adenocarcinoma	70	62	17	27.4	10	11	2
Alveolar adenocarcinoma	40	34	8	23.5	5 *	1	5
Undifferentiated carcinoma	25	10	5	50.0	3	0	2
Sarcoma	3	1	0	--	--	--	--
Squamous-cell carcinoma	1	1	0	--	--	--	--

* Includes one mediastinal extension.

TABLE 8.—*Analysis of Deaths Due to Thyroid Cancer*

Pathology	Total Cases, No.	Over-All Deaths Due Directly to Thyroid Cancer,* No.	Resectable Cases, † No.	Deaths Due to Thyroid Cancer in Resectable Patients	
				No.	%
Papillary adenocarcinoma	70	9	62	4	6.4
Alveolar adenocarcinoma	40	7	34	4	11.8
Undifferentiated carcinoma	25	13	10	2	20.0
Sarcoma	3	2	1	0	—
Squamous-cell carcinoma	1	0	1	0	—

* Includes deaths of unknown cause and also those due to other causes with thyroid cancer still present.
† Patients who had curative surgery applied to a resectable lesion.

62 patients with an average follow-up of 7.4 years (median 5.4 years). The recurrence rate in cervical nodes was found to be 17%, and the local thyroid recurrence was 16%. Some recurrences were in both locations. Distant metastases developed in only 3%. In a smaller number of patients with resectable alveolar adenocarcinomas, the recurrence rate was 23.5%. The average follow-up period was 6.3 years (median 5.1 years). Distant metastases were more frequent as a source of recurrence (14.7%) than they were in the papillary group, whereas local thyroid recurrence occurred in about the same incidence (14.7%) and local node recurrence was less frequent (3%). The greater tendency of the alveolar type to metastasize distally is obvious.

The number of resectable cases of undifferentiated carcinoma was small, as might be expected (40%), and the recurrence rate was very high (50%). This highly malignant variety recurred locally in the thyroid and in distant metastases.

The data in Table 8 show the deadliness of this disease in patients who originally were considered to be adequately treated. Again these data include all deaths regardless of length of follow-up study. The surgery primarily applied in all of these cases consisted of subtotal thyroidectomy only. The chronicity of thyroid cancer is apparent from an average survival of five years for the four patients dying directly of papillary adenocarcinoma, seven years for the four dying of alveolar adenocarcinoma and six years for the two dying of undifferentiated carcinoma. The location of the recurrent cancer and the cause of death in these patients are listed in Table 9. Of the 10 cases of death local recurrence occurred in 7, cervical node recurrence in 1, and distant metastases in 4. Note that the single case of cervical node recurrence did not cause the death in that patient.

It is seen from this analysis that in a short average follow-up period there was a respectable local thyroid gland area and

TABLE 9.—*Site of Recurrence in Patients Dead of Thyroid Carcinoma After Curative Resection*

	Total	Site of Recurrence			
		Local Thyroid	Cervical Nodes	Distant Metastases	Unknown *
Papillary adenocarcinoma	4	3	1	1	1
Alveolar adenocarcinoma	4	2	0	2	1
Undifferentiated carcinoma	2	2	0	1	0
Total	10	7	1	4	2

* Died with thyroid status unknown.

cervical node recurrence in the papillary adenocarcinoma type and thyroid gland and distant metastatic recurrence in the alveolar adenocarcinoma and undifferentiated types. The distant metastases, unfortunately, are out of the range of further surgical therapy. They can be treated surgically only by prevention. The possible multicentric origin of thyroid cancer and the shown propensity for local gland recurrence are evidence for the need for a radical local thyroid gland resection with all pathological types. Such a procedure might eliminate part or all of the local thyroid recurrences and possibly also prevent secondary metastases from such residual disease.

The question arises whether radical neck dissection in the absence of clinical neck node involvement is a necessity. We found cervical node recurrence in 11 of 52 patients with papillary adenocarcinoma who had not originally been given a radical neck dissection, an incidence of 21.1%. Frazell and Foote[3] found that 61.2% of a series of 67 patients with papillary adenocarcinoma who were given a prophylactic radical neck dissection had histologic node metastases. There is evidence, therefore, that occult foci occur in a high percentage of cases, and it has been shown here that they do not remain subclinical forever. With a longer follow-up period, our figure for cervical node recurrence might well approach that of Frazell and Foote. Of great immediate importance is whether these residual, asymptomatic foci might not be extending out beyond the reach of further surgery, either by direct extension or by seeding of distant metastases. Should not such nodes in papillary adenocarcinoma hidden from touch and sight therefore be resected primarily? Might not such initial radical surgery at the very least prevent the risk of multiple operative procedures? The fact that papillary adenocarcinoma occurs with high frequency early in life is further indication for an initial radical approach.

Summary

The results of surgical treatment of 139 cases of cancer of the thyroid have been analyzed in a series similar in pathological classification and survival to the series reported in the literature. Because of the chronicity of the papillary and alveolar types, the results of the relatively conservative surgery applied were further evaluated by study of the pathogenesis of recurrences and death. For a short average follow-up period a high incidence of recurrence was found in the local thyroid gland area and in cervical nodes of patients with papillary adenocarcinoma and required multiple operative procedures. A similar high incidence of recurrence was found in the local thyroid area of patients with alveolar adenocarcinoma and undifferentiated carcinoma. Distant metastases also were frequent in the latter groups. Death in all pathological types was found to be associated either with local recurrence and with extension or distal metastases and cachexia. The need for more radical primary surgery to the thyroid and cervical nodes was felt to be indicated.

Department of Surgery, The Johns Hopkins Hospital (5).

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Operative Techniques for Repair of Various Types of Diaphragmatic Hernia

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In the surgical repair of diaphragmatic hernia, this question frequently arises: "What operative technique should be utilized, and should the approach be abdominal or thoracic?" The surgeon who repairs diaphragmatic hernias should be familiar with the pathological anatomy of the various types of hernia and applicable techniques of repair, as well as capable of utilizing either an abdominal or a thoracic approach, the choice of which depends on the individual patient's problem.

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The operative techniques described here were found to be most satisfactory in the repair of various types of diaphragmatic

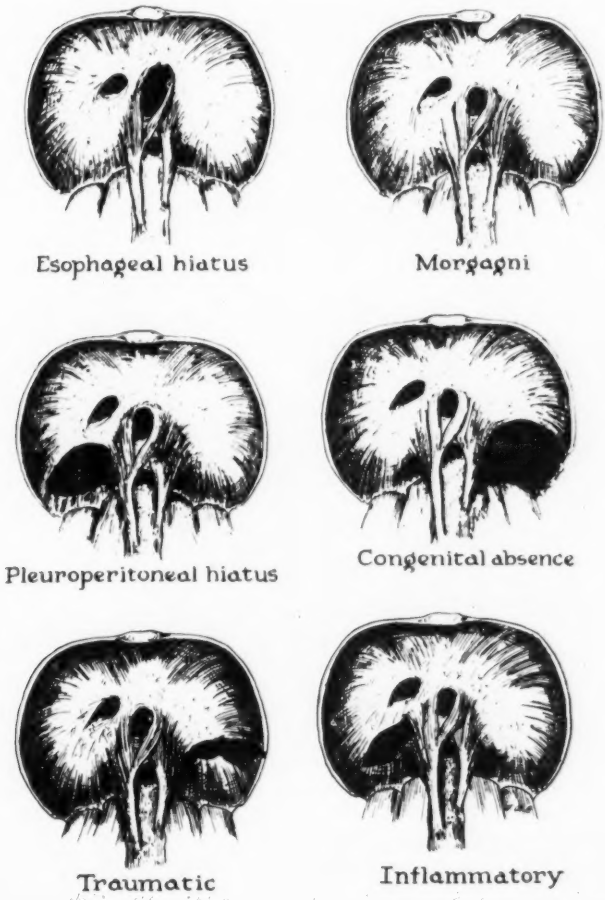


Fig. 1.—Diagrammatic view of diaphragm from abdominal aspect, showing locations of acquired, congenital, and traumatic defects which may result in diaphragmatic hernias. Note that esophageal hiatus is produced by fibers from the right crus of the diaphragm.

hernias occurring in 109 patients observed from 1935 to 1956.

The embryonic development of the diaphragm, which is from several different segments fusing to form one structure, containing three natural openings, contributes to developmental anomalies, weak areas, or actual defects. There may be improper fusion, lack of firmness, or absence of an entire leaf, resulting in either a weakened or an abnormally enlarged opening, i. e., parasternal hernia through the foramen of Morgagni (Fig. 1).

Anatomical studies I have made using fresh and preserved cadaver material confirm the observations of Allison,[2] who was the first surgeon to demonstrate that the muscle fibers which form the esophageal hiatus of the diaphragm arise from the right crus, which is larger than the left, and that fibers from the right crus form both the right and the left margin of the hiatus. The right crus has its origin in stout, tendinous bands from the inferior and lateral surfaces of the first three or four vertebrae and their fibrocartilages. The deep and superficial fibers of the right crus come together anteriorly in close proximity to the inferior phrenic vein and tendinous portion of the diaphragm; this closes the hiatus tightly anteriorly and laterally, but posteriorly it is occluded by only a few decussating muscle fibers and fibroareolar tissue (Fig. 2).

The left crus arises from the upper two lumbar vertebrae and is less well developed than the right. In none of the cadavers dissected has it been demonstrated that the left crus contributes to the formation of the hiatus of the esophagus, as shown in

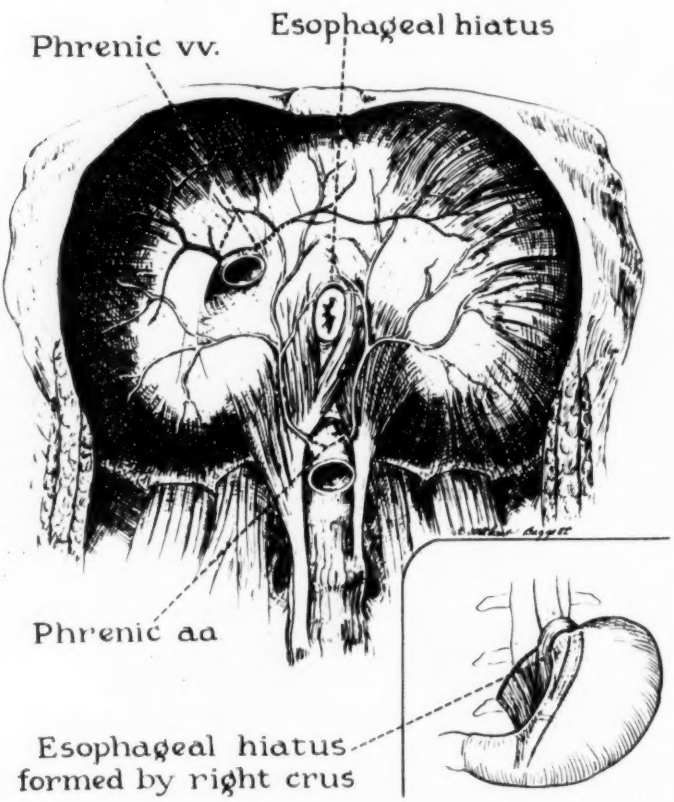


Fig. 2.—Diagrammatic representation of cadaver specimen from abdominal aspect, demonstrating that esophageal hiatus is formed by splitting of the muscle fibers of the right crus of the diaphragm, which is larger and stronger than the left crus, and is only lightly reinforced by fibers from the left crus.

standard textbooks on anatomy prior to 1956.

Phrenoesophageal Ligament

During the anatomical studies of cadaver material, the fascial relation of the lower esophagus, cardia, and diaphragm was established thus: The thin, but definite, fascial lining of the abdomen (the fascia transversalis) extends onto the undersurface of the diaphragm and is attached to its musculature by loose areolar connective tissue. It then extends through the esophageal hiatus, where it joins the endothoracic fascia on the superior surface of the diaphragm and is attached to the fascia propria 3 or 4 cm. above the esophagogastric junction. The abdominal component, which is the strongest portion of this fascia, has been designated as the phrenoesophageal ligament[2] (Fig. 3).

The esophagus passes through a muscle sling composed of decussating fibers of the right crus of the diaphragm, which is formed around the cardia. This muscle sling and the phrenoesophageal ligament, unless they become weakened, maintain the esophagogastric junction below the diaphragm. The esophageal hiatus must be large enough to permit passage of food into the stomach, and the lower end of the esophagus must be so anchored to the dia-

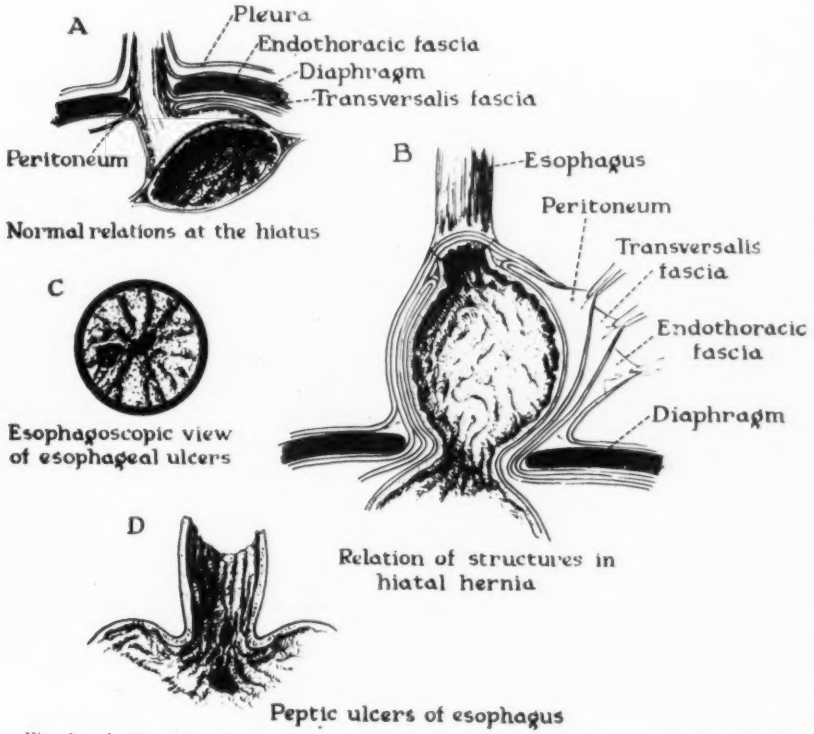


Fig. 3.—*A*, diagrammatic representation of the normal anatomical relation of the esophagogastric junction and diaphragm. The phrenoesophageal ligament is formed by the fascia transversalis and endothoracic fascia and is attached to the fascia propria of the esophagus 2 or 3 cm. within the thoracic cavity.

B, diagrammatic representation of a sliding hiatal hernia. The weakened phrenoesophageal ligament becomes stretched. The hiatus becomes enlarged, permitting the lower end of the esophagus and the cardiac end of the stomach to extend into the posterior mediastinum, allowing regurgitation of acid and peptic gastric contents to produce esophagitis.

C, ulcers of lower esophagus and cardia viewed esophagoscopically.

phragm that the stomach cannot be drawn up into the chest during normal respiration. However, if factors develop in which the hiatus becomes enlarged and the phrenoesophageal ligament becomes attenuated and weakened, the normal positive abdominal pressure and negative thoracic pressure, in conjunction with the pull of the longitudinal muscles of the esophagus, will result in displacement of the cardia into the posterior mediastinum.

Some surgeons utilize the abdominal approach for the repair of diaphragmatic hernia for the following reasons: (1) The absence of intercostal pain following operation is desirable; (2) laparotomy is thought to be better tolerated by most patients than thoracotomy, and (3) this approach enables the surgeon to determine whether other abdominal pathology is present and, if so, to correct it. The abdominal approach was used in 13 patients who had other pathology of the upper abdomen which required surgical correction. Cholecystectomy was performed for cholelithiasis in six patients, and seven, with either duodenal or gastric ulcer of sufficient seriousness to require surgical correction, had subtotal gastrectomy.

I prefer a transthoracic approach in the repair of diaphragmatic hernia for the following reasons: (1) The esophagus is more easily mobilized by direct vision than blindly; (2) better exposure of the hiatal contents is possible; (3) the type of hernia present, i. e., sliding, paraesophageal, or esophagoaortal hernia or congenital short esophagus, is more easily determined; (4) reconstruction of the esophagogastric junction below the diaphragm is more readily carried out; (5) the thoracic incision may be more easily extended into the abdomen, when necessary, than an abdominal incision may be extended into the chest, and (6) the phrenic nerve, *which is never crushed as a therapeutic measure in hiatal hernia,* may be injected with 1% procaine hydrochloride solution at the time of repair of the hernia to permit a more satisfactory convalescence; this cannot be carried out through an abdominal approach.

Early ambulation and placing the patient in a semierect position by elevation of the head of the hospital bed permits even those who might be considered poor surgical risks to make a normal convalescence.

Types of Hernia Repair

Repair of Sliding Hiatal Hernia.—In sliding hiatal hernia it is important to reconstruct the phrenoesophageal ligament after reduction of the hernia and then reduce the size of the hiatus. Repair of diaphragmatic hernia through the thoracic approach was carried out in 86 patients, using the following method: The patient is placed in a right lateral prone position, and the pleural cavity is opened through the eighth inner space (Fig. 4*A*, *B*). It has been my practice for several years to incise the eighth rib, anteriorly and posteriorly, and turn it up as a trap door, along with the intercostal muscles. The left lung is deflated, retracted upward, and retained in this position with the use of a saline gauze pack. Extensive adhesions between the lung and the parietal pleura were present in eight patients who had had pulmonary inflammation involving the lower lobe of the lung. If the lung parenchyma is injured in dividing these adhesions, care must be exercised to repair it properly to prevent tension pneumothorax following the surgical procedure.

The left phrenic nerve, celiac plexus, and posterior mediastinum are infiltrated with 1% procaine hydrochloride solution. An incision is made in the posterior parietal pleura from the pericardium to the thoracic spine. A vertical incision is made through the pleura from the horizontal incision over the hernial sac to a sufficient height to expose the hernia (Fig. 4*C*). The pleural flaps are dissected widely, exposing the lower esophagus, hernia, and phrenoesophageal ligament. The esophagus is dissected out at the upper angle of the wound, and a Penrose drain is placed around it for trac-

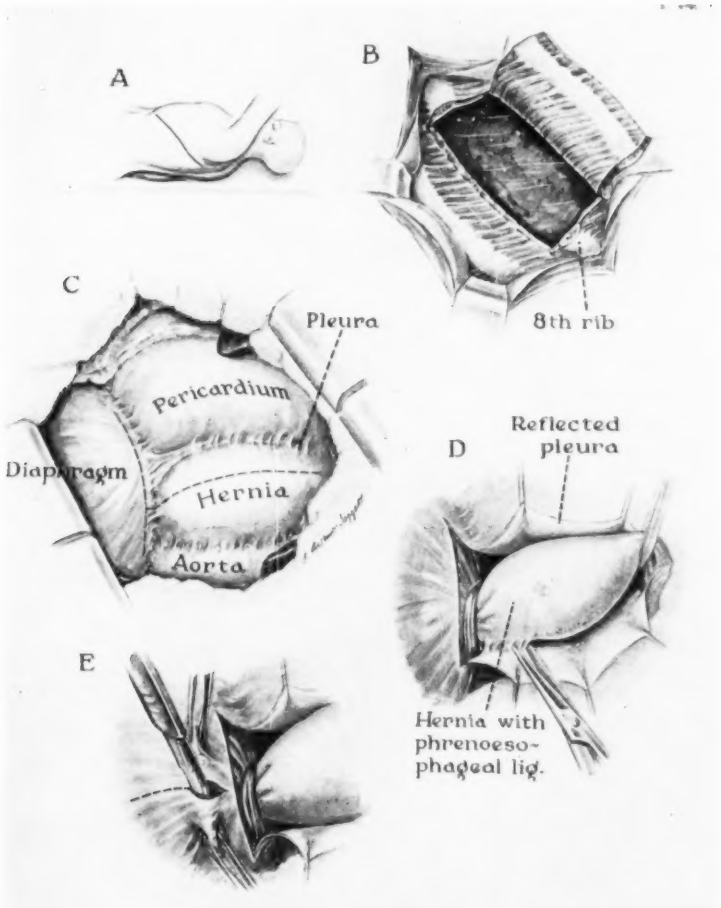


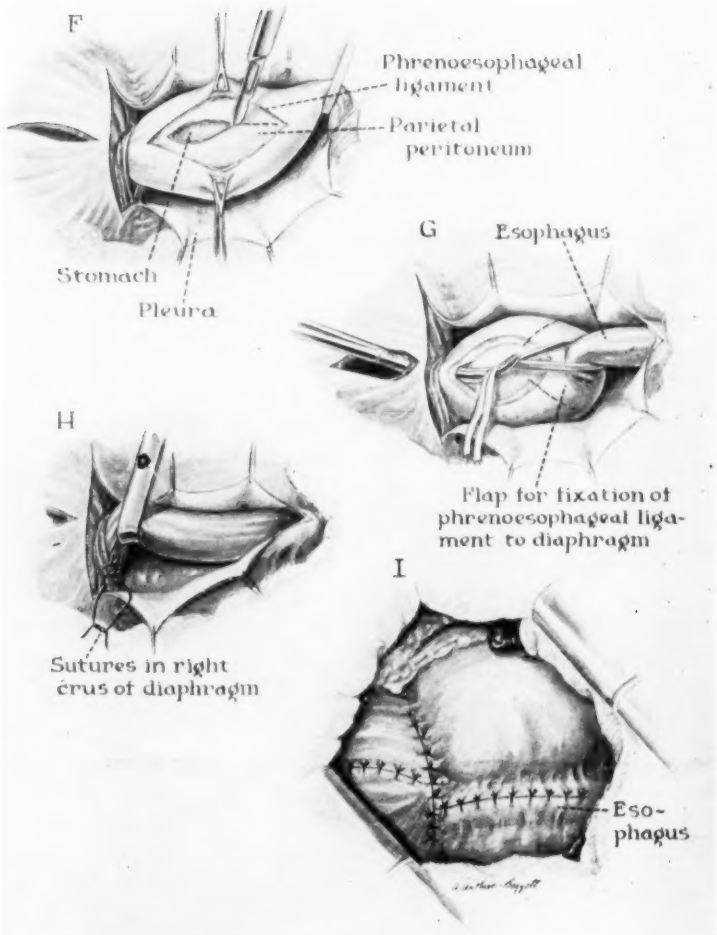
Fig. 4.—*A*, *B*, operative technique for repair of sliding hiatal hernia. The patient is placed in a right lateral prone position. An incision is made between the eighth and the ninth rib. The eighth rib is severed at the costochondral junction and at the posterior angle of the incision. The rib and soft tissues are turned up as a trap door. The lower lobe of the left lung is deflated and packed off with a saline pack. The phrenic nerve is injected with 1% procaine hydrochloride solution but is *not* crushed.

C, an incision is made through the parietal pleura, beginning anteriorly between the pericardium and the diaphragm and extending posteriorly to the aorta. A longitudinal incision is made over the hernial sac and extended upward to the inferior pulmonary ligament. The pleural flaps are dissected widely over the esophagus.

D, the upper end of the esophagus and the vagus nerve are dissected out. A Penrose drain is placed around the upper end of the esophagus for traction. The lower esophagus, containing the herniated stomach, is dissected from surrounding structures, exposing the musculature of the right crus, which forms the hiatus.

E, the left leaf of the diaphragm is tented with Allis forceps, and a radial incision is made through it, 6 to 8 cm. from the hiatus.

tion (Fig. 4*D*). The hernial sac and esophagus are dissected from surrounding structures; by retracting the esophagus, the crura of the diaphragm on each side can be dissected out and their fibers demonstrated. The dome of the left diaphragm, approximately 8 cm. from the hiatus, is tented with Allis forceps, and a radial incision of suffi-



F, the index finger of the left hand is extended through the rent in the diaphragm and hiatus; the phrenoesophageal ligament is then severed around the esophagus, leaving a cuff of tissue 3 to 4 cm. from its attachment to the esophagus.

G, the Penrose drain around the upper end of the esophagus is caught by a curved Kelly clamp (inserted through the rent in the diaphragm) and pulled downward, replacing the stomach within the peritoneal cavity.

H, the method used to close the esophageal hiatus. The muscle fibers of the right crus are sutured together with three or four sutures of medium-size silk.

I, the parietal pleura is closed with interrupted fine silk sutures.

cient length to give good exposure is made through the fibers of the diaphragm (Fig. 4*E*). The phrenoesophageal ligament is tented with Allis forceps, and an incision is made through it; an incision is also made around its entire circumference approximately 3 to 4 cm. from the esophagus (Fig. 4*F*). The Penrose drain is grasped by a Kelly clamp inserted through the rent in the diaphragm and pulled downward, reducing the hernia and replacing the esophagogastric junction beneath the diaphragm (Fig. 4*G*). The phrenoesophageal ligament is sutured to the diaphragm by one of several methods, all of which are based on the original devised by Allison.[2] Johnsrud[4] and Sweet[6]

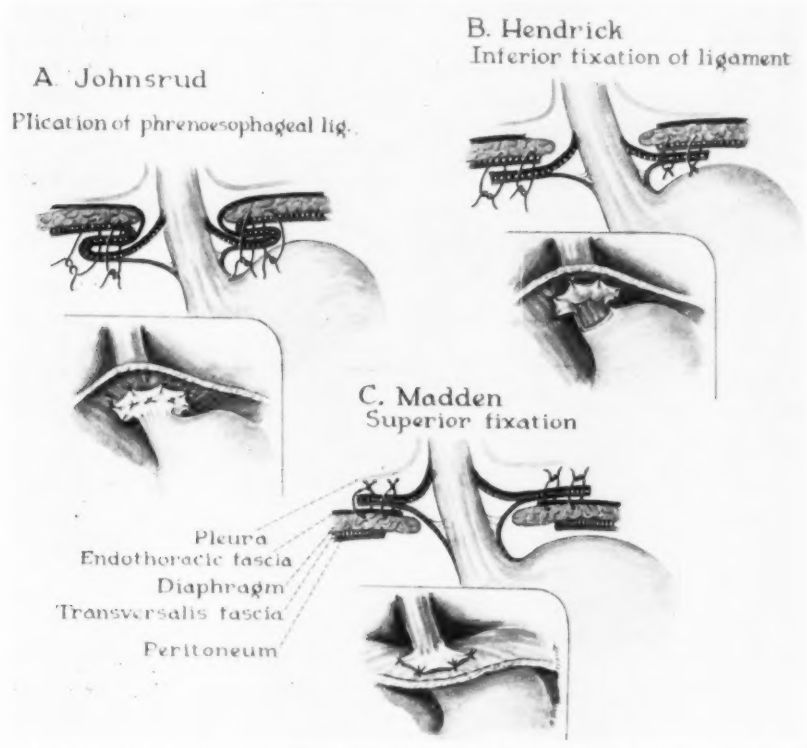


Fig. 5.—*A*, the various methods of anchoring the phrenoesophageal ligament to the diaphragm and reestablishing the esophagogastric junction beneath the diaphragm are based on that developed by Allison. The method of Johnsrud and Sweet, in which the phrenoesophageal ligament is plicated on each side and sutured to the undersurface of the diaphragm, eliminating all redundant phrenoesophageal ligament, is a satisfactory method.

B, I suture the cuff of the phrenoesophageal ligament to the undersurface of the diaphragm with interrupted sutures of medium-size silk.

C, the method of Madden is suturing the phrenoesophageal ligament to the superior surface, rather than to the undersurface of the diaphragm. This method is simpler than that of Johnsrud, particularly in thick-chested patients. Any one of these methods, if properly performed, gives good results by anchoring the esophagus in its normal position and reestablishing the cardia beneath the diaphragm.

plicate the phrenoesophageal ligament and suture it to the undersurface of the diaphragm (Fig. 5*A*). Madden [5] sutures the severed edge of the phrenoesophageal ligament to the superior surface of the diaphragm (Fig. 5*C*). The method I use most frequently is to suture the phrenoesophageal ligament to the undersurface of the diaphragm with five or six interrupted silk sutures, which are extended around the cardia as far as possible to reestablish the esophagogastric junction in its normal position (Fig. 5*B*).

The Penrose drain is then removed from around the cardia, and the rent in the diaphragm is closed with interrupted silk sutures. The posterior angle of the esophageal hiatus is closed by suturing the muscle bundles of the right crus, which form the left and right margins of the hiatal ring, with interrupted medium-size silk sutures (Fig. 4*H*). The index finger is placed through the hiatus beside the esophagus (which contains a Levin tube) to prevent the hiatus from being closed too tightly. The

parietal pleura is closed with interrupted fine silk sutures (Fig. 4*I*).

Repair of Paraesophageal Hiatal Hernia.—In paraesophageal hiatal hernia, as well as those defects in other areas of the diaphragm, it is essential to reduce the hernia, eliminate the sac, if present, and repair the defect. In this type of hernia the esophagus is still firmly anchored to the diaphragm; the hernial sac containing the stomach and/or other abdominal viscera ascends into the posterior mediastinum adjacent to the esophagus (Fig. 6*A*).

The transthoracic approach is used in the repair of paraesophageal hiatal hernias. An incision is made in the parietal pleura (Fig. 6*B*); the esophagus is dissected out and a tape placed around it for traction (Fig. 6*C*). A radial incision is made in the left leaf of the diaphragm (Fig. 6*D*); the hernial sac is dissected from the esophagus (Fig. 6*E*). The index finger is placed through the rent in the diaphragm beside the esophagus and stomach; an incision is made through the hernial sac (Fig. 6*F*). A Kelly clamp is inserted through the rent in the diaphragm and hiatus through which the tape is pulled, thereby replacing the stomach and/or other abdominal viscera in the peritoneal cavity. The peritoneal sac is ligated at its base and transfixed to the undersurface of the diaphragm (Fig. 6*G*, *H*). The rent in the diaphragm is closed with interrupted silk sutures. The posterior angle of the esophageal hiatus is closed by suturing the left and right margins of the hiatal ring together with interrupted sutures of silk (Fig. 6*I*). The parietal pleura is closed with interrupted fine silk sutures (Fig. 6*J*).

Repair of Esophagoaortal Hiatal Hernia.—The defect resulting from esophagoaortal hiatal hernia occurring in two patients in this series extended anteroposteriorly from the esophageal hiatus to the aortal hiatus and was readily exposed by the method previously described (Fig. 4*A*, *B*). Adams and Lobb[1] report that this type of hernia may be completely obscured within the mediastinum. The mediastinal pleura is opened; the esophagus is identified and dissected out, and a Penrose drain is placed around it for traction (Fig. 4*D*). The hernia, which is located in the mediastinum posterior to the heart, is dissected from the pleura on both sides. The hernial sac in both patients was of considerable size. An incision is made in the left leaf of the diaphragm (Fig. 4*E*); the sac is delivered from the thoracic cavity into the abdominal cavity and ligated at its base with medium-size silk sutures and transfixed to the undersurface of the diaphragm (Fig. 6*G*). The left segment of the right crus, which normally forms the left margin of the esophageal hiatus, was found to be thinned out, with only a few strands of muscle fibers remaining. In repairing the defect, the right and left crura are sutured together with interrupted silk sutures, which are placed snugly around the aorta and loosely around the esophagus to prevent stricture.

Repair of Hernia Through the Foramen of Morgagni, or Substernal Hernia.—Herniation through the left foramen of Morgagni occurred in two patients in this group. Surgical reduction and repair of these were carried out through a transabdominal approach, using an upper transverse incision with the convexity slightly upward. The hernial contents were reduced. The peritoneal sac was ligated at its base, and the redundant portion was excised. The margin of the defect in the diaphragm was sutured to the posterior rectus sheath of the anterior abdominal wall. The round and falciform ligaments of the liver were incorporated in the closure, adding strength to the repair.[3]

A thoracic approach should be utilized for repair of this type of hiatal hernia if the defect is through the right foramen of Morgagni.

Repair of Diaphragmatic Hernia Resulting from Either Direct or Indirect Trauma, Inflammatory Necrosis of the Diaphragm, or Congenital Absence of One Segment of the Diaphragm.—When a hernia is present

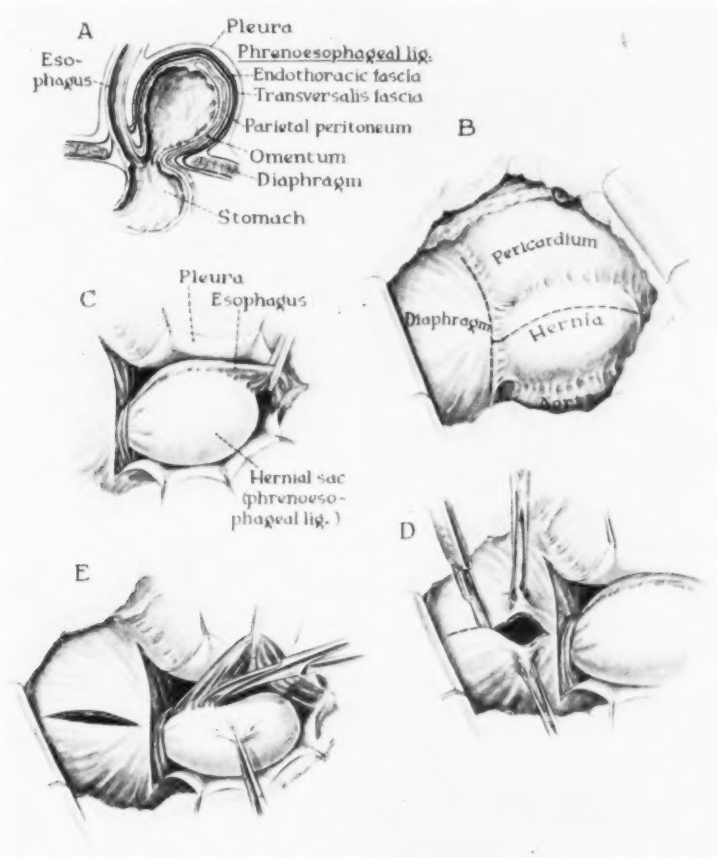


Fig. 6.—*A*, paraesophageal hiatal hernias are frequently large and contain the stomach and/or other abdominal viscera. The esophagus is retained in its normal position in relation to the diaphragm; there is herniation of a considerable segment of stomach into the posterior mediastinum adjacent to the esophagus.

B, a T-shape incision is made through the parietal pleura between the pericardium and the diaphragm; it is extended posteriorly to the aorta, with the longitudinal portion extending over the hernial sac.

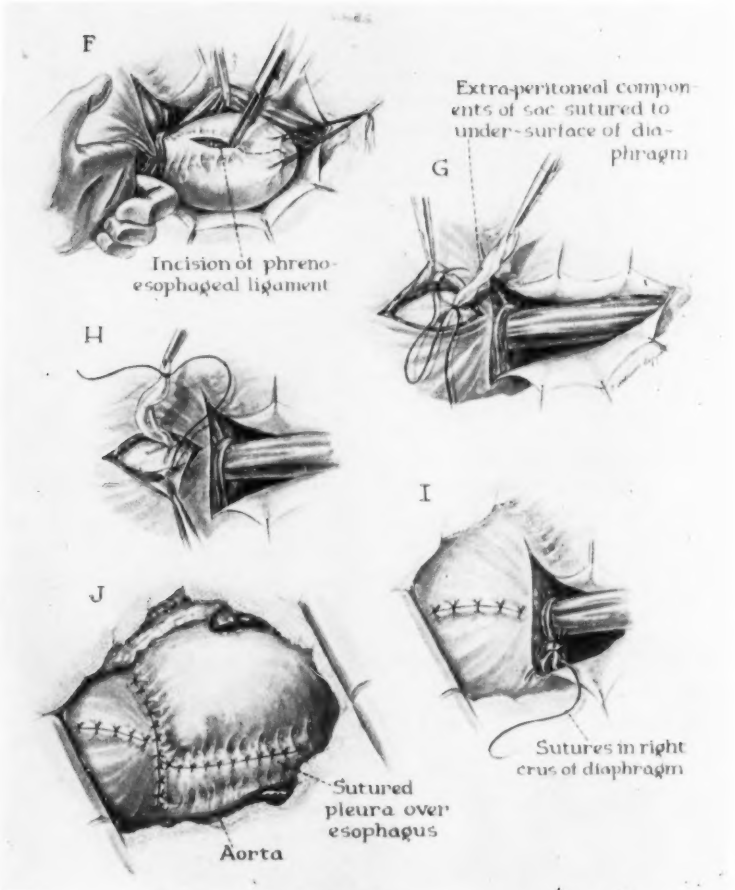
C, the upper end of the esophagus is dissected out, and a Penrose drain is placed around it for traction.

D, the left leaf of the diaphragm is tented with Allis forceps, and a radial incision is made in it, beginning 6 to 8 cm. from the hiatus.

E, the hernial sac is dissected out on all sides and freed from the esophagus.

through the right side of the diaphragm, a right thoracic approach is utilized, owing to the large right lobe of the liver, which interferes with exposure in an abdominal approach. If the left side of the diaphragm is involved, the repair may be carried out through either a left thoracic or an abdominal approach. There were four patients with traumatic hernia in this group; two of the hernias were repaired transabdominally and two through a left transthoracic approach.

After reduction of the hernia the defect in the diaphragm is readily repaired. In one patient the spleen, which was strangulated, was removed. In another, whose hernia re-



F, the hernial sac is incised over the index finger, which is extended through the rent in the diaphragm and hiatus; the hernia is reduced.

G, the hernial sac is ligated at its base with medium-size silk sutures; the sac is sutured to one edge of the diaphragm.

H, the excess hernial sac is excised, and any remaining portion is sutured to the undersurface of the diaphragm, reestablishing the normal physiology of the cardia.

I, the muscle fibers of the right crus, which form the hiatus, are sutured together with medium-size silk sutures.

J, the parietal pleura is closed with interrupted fine silk sutures.

sulted from indirect trauma produced by the steering wheel of an automobile, a segment of omentum, which was strangulated, was removed.

There were four patients in whom a substantial segment of diaphragm was absent: One defect resulted from amebic abscess of the right lobe of the liver; the second, from a subphrenic abscess on the left side, and the third and fourth, from congenital absence of a segment of the diaphragm. Reinforcement with strips of fascia lata, approximately 6×8 cm., was made after repair of the defect. No reaction occurred from the use of the fascia lata.

Summary and Conclusions

Satisfactory operative techniques for the repair of various types of diaphragmatic hernias in 109 patients are described.

A comprehensive knowledge of the pathological anatomy of the various types of diaphragmatic hernias is essential in their repair. The transthoracic incision permits better exposure of the operative field and is more frequently utilized than is the abdominal approach, which is used only in certain instances.

Dr. J. S. P. Beck and Dr. Louis S. Graham Jr., Department of Pathology, Druid City Hospital, Tuscaloosa, Ala., and Dr. Carl E. Sensenig, Department of Anatomy, Medical College of Alabama, Birmingham, furnished fresh and preserved cadaver material for adequate study of the lower esophagus, cardia, and diaphragm.

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Results of Treatment of Diaphragmatic Hernia

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Diaphragmatic hernia has been termed "the great masquerader" and is second only to duodenal ulcer in the frequency with which it presents symptoms involving the upper gastrointestinal tract. Roentgenographic and esophagoscopic studies, in conjunction with an accurate history, of patients with upper gastrointestinal and/or lower thoracic pain often demonstrate a diaphragmatic hernia as the offender. Brick[3] reports that a diagnosis of hiatal hernia is made in approximately 9% of patients who have roentgenographic examination of the upper gastrointestinal tract.

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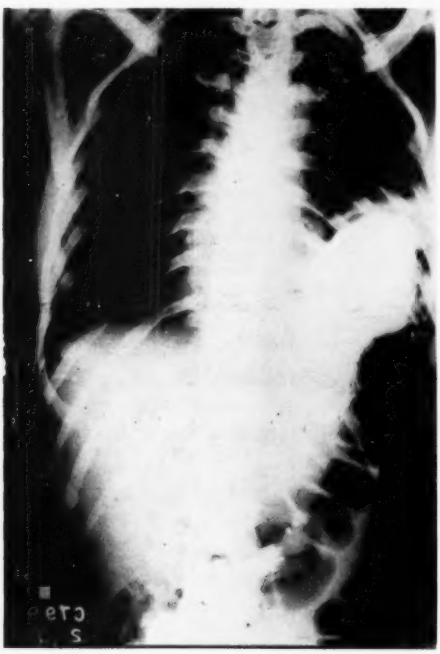
Fig. 1A.—Traumatic diaphragmatic hernia through the left leaf of the diaphragm produced by shrapnel wound received by the patient in World War II. The patient was admitted with a partial intestinal obstruction. The spleen, splenic flexure of the colon, omentum, and stomach were within the left thoracic cavity.



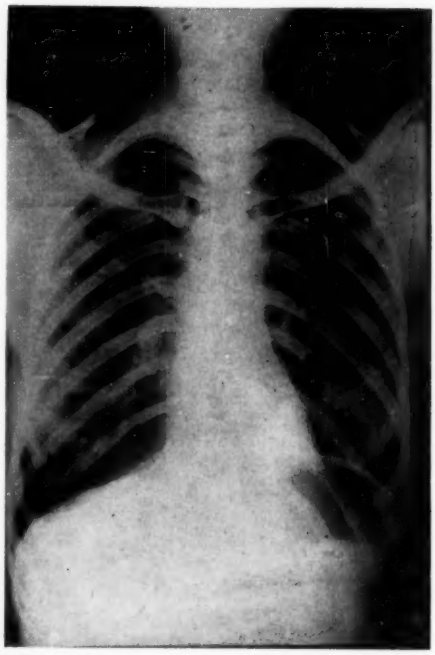


Fig. 1B.—Roentgenogram demonstrating the structures in their normal position within the peritoneal cavity following surgical correction of the traumatic diaphragmatic hernia shown in *A*.

Roentgenologists and gastroenterologists who observe hiatal hernias during routine studies of the upper gastrointestinal tract seem prone to minimize these findings. On the other hand, the surgeon who observes the patient after serious complications develop may logically conclude that all diaphragmatic hernias are dangerous, and his concern for patients affected with these hernias, as well as those occurring elsewhere in the body, is based on complications encountered, i. e., incarceration, obstruction (Figs. 1A and 1B), strangula-

TABLE 1.—*Data on 109 Patients with Diaphragmatic Hernia Treated Surgically from 1935 to 1957*

Site of Hernia	No. of Patients	Contents of Hernia	No. of Patients
1. Esophageal hiatus			
(*a*) Sliding hiatal	86	Stomach	86
(*b*) Paraesophageal	9	Stomach	3
		Stomach and spleen	2
		Stomach, colon, and omentum	4
(*c*) Congenital short esophagus	2	Stomach	2
(*d*) Esophagoaortal	2	Stomach	2
2. Foramen of Morgagni (substernal)	2	Small bowel	1
		Transverse colon	1
3. Traumatic			
(*a*) Direct (stab or shrapnel)	3	Stomach	1
		Stomach and omentum	1
		Spleen and colon	1
(*b*) Indirect (steering wheel of automobile)	1	Omentum and colon	1
4. Inflammatory			
(*a*) Following amebic abscess of liver	1	Omentum and colon	1
(*b*) Following left subdiaphragmatic abscess	1	Spleen and colon	1
5. Congenital absence of portion of diaphragm	2	Stomach, spleen, and colon	2
Total	109		109

tion of involved viscera, and, in those patients with sliding hiatal hernia, esophagitis, stricture, and hemorrhage of the lower esophagus. Blades and Hall[2] report the chief complications of hiatal hernia to be esophagitis, stricture, and hemorrhage.

Since complications of this common lesion occur more frequently in older patients, it would seem to be a safe assumption that these conditions will be encountered more frequently in the future, owing to an increase in the number of older patients in the population.

From 1935 to 1956, a total of 276 patients were observed in whom a diagnosis of herniation through the diaphragm was established by roentgenographic and esophagoscopic examination. This report includes the clinical histories, operative findings, results of treatment, and follow-up examinations on approximately 90% of 109 of the 276 patients with symptoms sufficiently serious to require surgical treatment (Table 1). The age range of these patients was from 12 to 79; 24 were under 40 years of age, and more than 50% of the group were past the age of 50 (Table 2).

Symptoms

Opinions vary concerning the frequency with which diaphragmatic hernias produce symptoms. Allison[1] estimates that at least 75% of all hiatal hernias produce significant symptoms and 50% develop serious complications if permitted to persist. The symptoms in this group of patients varied (Table 3); in some they were of short duration. Four patients, under 45 years of age, whose symptoms had been present less than 18 months, had exsanguinating bleeding from a strictured, ulcerated esophagus which required resection of the involved segment.

Diagnosis

A careful clinical history and roentgenographic study of the thoracic cavity and gastrointestinal tract have demonstrated the

TABLE 2.—*Age Range of 109 Patients with Diaphragmatic Hernia Treated Surgically from 1935 to 1957*

Age of Patients, Yr.	No. of Patients
12 to 29	8
30 to 39	16
40 to 49	28
50 to 59	30
60 to 69	18
70 to 79	9
Total no. of patients	109
Total no. of male patients	48
Total no. of female patients	61
Age of youngest patient	12 yr.
Age of oldest patient	79 yr.

TABLE 3.—*Symptoms of 109 Patients with Diaphragmatic Hernia Treated Surgically from 1935 to 1957*

Symptoms		No. of Patients
1. Pain		172
(*a*) Abdominal	68	
Left upper	12	
Epigastric	50	
Right upper	6	
(*b*) Thoracic	54	
Substernal	38	
Precordial	16	
(*c*) Referred	50	
Neck	22	
Back	12	
Shoulders and arms	16	
(*d*) Postural relief from pain		42
Prone position	4	
Standing or sitting	38	
2. Vomiting		51
3. Dyspnea		63
4. Intestinal obstruction		17
5. Dysphagia		26
(*a*) Mild	10	
(*b*) Severe	16	
6. Bleeding		58
(*a*) Severe recurrent	14	
(*b*) Chronic resulting in continuous anemia	44	
Patients whose symptoms had been mistaken for coronary artery disease		18
Patients in whom other disease also present		20
(*a*) Coronary artery disease	5	
(*b*) Cholelithiasis	6	
(*c*) Duodenal ulcer	4	
(*d*) Gastric ulcer	3	
(*e*) Diverticulitis, left colon	2	

frequency with which the various types of diaphragmatic hernias occur. An accurate diagnosis may be established by requesting a careful roentgenographic investigation of the lower esophagus and cardia while applying pressure over the upper abdomen when the patient is in the Trendelenburg position. This technique should be part of the routine roentgenological examination of the upper gastrointestinal tract.

Seventeen patients in this series had undergone abdominal surgery elsewhere for symptoms which were not relieved until their diaphragmatic hernia was repaired. Three patients had gastroenterostomy, although roentgenographic studies later failed to reveal any evidence of peptic ulcer. Four patients had cholecystectomy, but only two had cholelithiasis; six had appendectomy for so-called chronic appendicitis. Four patients had exploratory laparotomy for severe recurrent gastrointestinal hemorrhage, but no diagnosis was established.

It should be emphasized that other abdominal pathology may be present with diaphragmatic hernia and serve as an etiological factor in producing symptoms. It is my practice to have roentgenological studies of the gastrointestinal tract and gallbladder, although a hiatal hernia is known to be present.

Gastrointestinal bleeding produced by hiatal hernia may be acute, recurrent, severe, painless, or insidious, resulting in chronic iron deficiency anemia. Blades [2] has demonstrated a definite relation between the duration of symptoms and the complications of bleeding and/or esophageal stricture. In general, when symptoms are of short duration in younger patients, bleeding and stricture are minimal. However, in older patients in whom symptoms have been present for more than five years, the incidence of intestinal bleeding and stricture formation is increased many times.

Intestinal bleeding occurred in more than 50% of this group of patients; in 14 it was

Fig. 2.—Patient with moderate-sized sliding hiatal hernia. Marked esophagitis is present; an ulcer with crater is shown involving the lower esophagus.

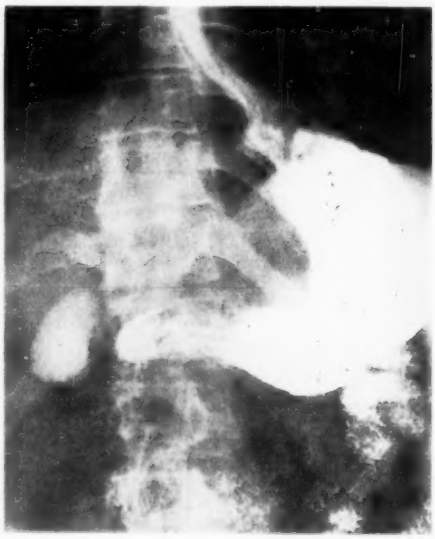


Fig. 3.—Lateral view of a large paraesophageal hiatal hernia containing practically the entire stomach and a segment of small bowel and transverse colon. The pylorus and cardia are pulled almost together; the greater curvature, small bowel, and an area of transverse colon form the topmost part of the hernial contents. This is commonly referred to as "upside-down stomach."

severe; in 6 there was massive hemorrhage which required transfusion to restore the blood volume before the hiatal hernia could be repaired. Stool examinations for occult blood were positive in 22 patients whose presenting symptoms were upper digestive distress and chronic anemia.

Esophagoscopic examination should be performed on patients with sliding hiatal hernia to determine whether esophagitis is present, whether there is significant shortening of the esophagus, or whether additional pathology is present. Thirty-eight patients had varying degrees of esophagitis; the mucous membrane was swollen and inflamed and appeared to be in folds. In a later stage of the disease the mucous membrane bled readily on contact with the esophagoscope, and not infrequently ulcers, varying in diameter from a few millimeters to 2 cm., were observed (Fig. 2). The cardia was lax and patulous, and in the more advanced stage of esophagitis there was marked spasm with stenosis. The disease progresses from this stage to fibrosis of the muscle layer with periesophagitis and stricture formation.

Of the 52 patients who had esophagoscopy, 5 had other pathology: Two patients had diverticula involving the lower fourth of the esophagus; one had lipoma, and one had squamous-cell carcinoma involving the esophagocardiac junction.

In many cases it is necessary to differentiate between coronary artery disease and hiatal hernia. The 18 patients in this group, 7 of whom had paraesophageal hiatal hernia (Fig. 3), 10 sliding hernia, and 1 esophagoaortal hernia, had been treated elsewhere for coronary artery disease. The facts that hiatal hernia and coronary artery disease are being diagnosed earlier and with increasing frequency and that both diseases occur in older or obese patients may make differentiation of the two difficult. Nuzum [4] reports that of 100 consecutive patients treated for angina pectoris, 25 were found to have hiatal hernias. It should be stressed that the two diseases may coexist and that it is important, in the presence of one, to rule out the other. Five patients with sliding hiatal hernias with marked esophagitis also had coronary artery disease.

TABLE 4.—*Types of Complications Encountered in Thirteen Patients Following Repair of Diaphragmatic Hernia*

Complication	No. of Patients
1. Vascular	
(*a*) Phlebothrombosis, left lower extremity (sublethal pulmonary embolism)	1
(*b*) Thormbophlebitis, right lower extremity	1
2. Pulmonary	
(*a*) Atelectasis, right	1
(*b*) Atelectasis, left	1
(*c*) Collection of serum in pleural cavity following thorocotomy, which required aspiration	6
3. Other	
(*a*) Periesophagitis and dysphagia	2
(*b*) Prostatic obstruction	1
Total	13

Complications Following Repair of Diaphragmatic Hernia

Thirteen patients developed complications following repair of various types of diaphragmatic hernias encountered (Table 4). One patient developed phlebothrombosis on the eighth postoperative day and had a sublethal pulmonary embolism, which was treated by ligation of the superficial femoral vein in the extremity involved. A second patient, who had large varicose veins, developed thrombophlebitis of the right lower extremity on the seventh postoperative day. This complication was treated by blocking the lumbar sympathetic chain on the involved side with 1% procaine hydrochloride solution.

Two patients developed atelectasis, one involving the lower lobe of the right lung and the second the lower lobe of the left lung. Prompt bronchoscopic aspiration of retained secretions gave immediate relief.

Six patients developed serum in the thoracic cavity, requiring aspiration following thoracotomy; in five of these there had been extensive adhesions between the lower lobe of the lung, the chest wall, and the diaphragm. In four of the six, repair of the diaphragmatic hernia was reinforced by the use of a segment of fascia lata.

Two patients, one of whom had congenital short esophagus and one a sliding hiatal hernia with marked esophagitis, developed periesophagitis and dysphagia. Each patient required esophageal dilatations for a period of six weeks following repair of the hernia.

A 76-year-old man with marked esophagitis resulting from a large sliding hiatal hernia, developed prostatic obstruction on the fifth postoperative day. Continuous catheter drainage was carried out; the patient developed cystitis, which was relieved by antibiotic and chemotherapy. The patient had a transurethral prostectomy one month following repair of the hiatal hernia.

Results of Repair of Diaphragmatic Hernias

On the 109 patients with various types of diaphragmatic hernia, 112 operative procedures were performed during the period from 1935 to 1956; the average postoperative hospital stay was 14 days. Postoperative roentgenographic studies of the intestinal tract were made on the majority of these patients, and a number, with sliding hiatal hernias, also had esophagoscopic examination.

Three patients with sliding hiatal hernias developed recurrences from one to five years following the first repair, and a second repair, using the technique of Allison,[1] was carried out with no further difficulty in any of the three patients. Ninety-five patients have been symptom-free following the operative procedure (Table 5). Eight patients continued to have symptoms referable to the upper gastrointestinal tract fol-

TABLE 5.—*Results of Repair of Diaphragmatic Hernia in 109 Patients Treated Surgically from 1935 to 1957*

Site of Hernia	No. of Patients	Degree of Relief			Recurrence	Lost to Follow-Up
		Complete	Partial	None		
Esophageal hiatus						
Sliding	86	78	2	0	3	3
Paraesophageal	9	7	1	0	0	1
Congenital short esophagus	2	1	1	0	0	0
Esophagomortal	2	1	1	0	0	0
Foramen of Morgagni	2	2	0	0	0	0
Traumatic	4	3	0	0	0	1
Inflammatory	2	1	1	0	0	0
Absence of segment of diaphragm	4*	2	2	0	0	0
Total	109	95	8	0	3	5

* Of the four defects, two were congenital.

lowing operation. Six of these had abdominal pathology corrected in addition to repair of diaphragmatic hernia: Two had cholecystectomy for cholelithiasis, and four had partial gastrectomy for duodenal or gastric ulcer. These patients had no further symptoms referable to diaphragmatic hernia but complained of some bloating and gaseous indigestion.

Two patients who had sliding hiatal hernias with marked esophagitis continued to have heartburn and gaseous indigestion following repair of the hernias. Both these patients had domestic problems which could have been contributory factors. Five patients were lost to follow-up one year following operation; when last seen, all five were symptom-free.

Summary

During the period from 1935 to 1956, observations were made on 276 patients in whom a diagnosis of herniation through the diaphragm was established by roentgenographic and esophagoscopic examination. Of this group, 109 patients, with symptoms of prolonged duration and severity, were treated surgically.

In general, patients with small asymptomatic hiatal hernias are not treated surgically. Older patients with hiatal hernias which are detected during routine roentgenological examination of the gastrointestinal tract are observed at regular intervals, and, if symptoms indicative of complications develop, surgical therapy is advised.

There were no operative deaths in this group of patients who had repair of various types of hiatal hernias. Three patients developed recurrences following repair of sliding hiatal hernias and had a second repair, after which all three have been symptom-free.

Ninety-five patients had complete relief of symptoms following repair of their hernias. Eight patients had some residual symptoms; in six of these the symptoms could be attributed to the presence of other abdominal pathology which was corrected at the time of the hernia repair. The other two patients had marked esophagitis present before a sliding hiatal hernia was repaired, and their residual symptoms could be referable to permanent changes in the muscular wall of the lower fourth of the esophagus.

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Histological Evaluation of Liver Biopsy Techniques

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To aid in the diagnosis of liver disease, punch biopsy techniques have been in use at the University of Michigan Hospital during the past six years. The information gained from such examinations has often been found diagnostic in itself, and also extremely useful when correlated with data from other laboratory studies and clinical examinations.

A review of the information gained from 107 punch biopsies of the liver during a five-year period (1951-1956) is presented here, together with similar data from 172 consecutive open biopsies of the liver during a three-year period (1953-1956). This review was undertaken to evaluate these procedures as performed and interpreted in this hospital and to attempt to establish criteria for their use.

The advantages of the punch biopsy are obvious: simplicity, economy, and avoidance of a general anesthetic. The chief disadvantages are possible hemorrhage, post-punch bile leaks, and difficulty in obtaining specimens adequate for histological interpretation. The open approach offers the distinct benefit of direct visual and palpable evidence for the diagnosis. This examination, of course, is not limited to the liver, which may reflect disease occurring elsewhere in the abdomen. With this method, areas of the liver can be selectively biopsied, whereas the punch method is necessarily a blind procedure. Hemorrhage and bile leaks should not be a problem, and the adequacy of the specimen is usually assured.

Data were obtained from the pathology reports and the chart for each individual case. No histological "second look" at the slides, with the benefit of complete laboratory and clinical findings, was attempted. The diagnoses recorded are those of the various members of the pathology staff who initially interpreted the slides. The only correlative information was that provided on the pathology requisition.

The punch-biopsy specimens were obtained by several members of the department of internal medicine. It should be noted that these specimens often represented initial biopsy attempts by these physicians. The submitted specimens, regardless of size, were all studied histologically. This series does not represent a selective one, where size of the specimens is an important factor and more exacting criteria for interpreting the material have been outlined.

Table 1 summarizes the histological interpretations of the submitted liver biopsy specimens. These data represent the impressions of the pathologists reading the slides and do not indicate the final clinical impression.

Punch Series

Positive histological diagnoses were made from 40 slides. Fourteen of these were malignant neoplasms. In 12 of the 14 cases

TABLE 1.—*Results of Histological Examination of Liver Specimens*

Diagnosis	Punch Biopsy	Open Biopsy
Positive	40 (37.3%)	169 (98.3%)
Probable or questionable	27 (25.2%)	2 (1.2%)
Misleading or wrong	10 (9.3%)	1 (0.5%)
None	30 (28%)	(0)
Total	108	172

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there was hepatomegaly which to the clinicians suggested neoplastic involvement. There were nine diagnoses of cirrhosis of varying types, and six cases of hemosiderosis. The remaining 11 cases represented infectious or toxic hepatitis (9 cases), von Gierke's disease (1 case), and fluid from an Echinococcus cyst (1 case).

The probable diagnoses usually involved specimens which were less than lobular in size and so did not permit the pathologist to arrive at a definite diagnosis, although the evidence suggested a diagnosis.

No diagnosis was rendered in 30 cases because of the inadequate size of the specimen, or because of disparity between the clinical findings and the histological material, which often showed only a few normal liver cells.

Open Series

The open-biopsy material yielded 169 positive histological pathology reports in 172 interpretations. The one case in error proved to be an intracanalicular bile-duct carcinoma, which had also been missed with a punch biopsy. This was a deep neoplasm, not visible on the liver surface.

Complications

There was significant intraperitoneal reaction in nine patients following the punch biopsy. One patient with far-advanced metastatic carcinoma died 38 hours following punch biopsy with moderately severe intraperitoneal hemorrhage. There was one instance of bile leak with bile peritonitis, requiring surgical closure of the defect in a distended common bile duct. The other patients required only conservative care.

In the open-biopsy series one patient died of cardiac arrest during the anesthesia induction. The final diagnosis in this case was Boeck's sarcoid with liver involvement.

TABLE 2.—*Positive Histological Punch-Biopsy Material*

Carcinoma	13
Lymphoma	1
Hemosiderosis	6
Cirrhosis	9
Portal	5
Biliary	2
Post-necrotic	2
Fatty liver	2
Cholangitis	4
Hepatitis	3
von Gierke's disease	1
Echinococcus cyst	1
	40

TABLE 3.—*Histological Diagnoses Later Proved To Be in Error*

Initial Diagnosis	Final Diagnosis
Polycystic disease	Bile-duct carcinoma
No recognizable liver tissue	Scirrhous carcinoma
Normal	Boeck's sarcoid
Normal	Malignant mesothelioma
Normal	Colon carcinoma
Normal	Nodular fibrosis
Normal (No diagnosis possible)	Medullary carcinoma
Cholangitis	Postnecrotic cirrhosis
Early cirrhosis	Contrast medium in Kupffer cells
Hyperchromatic cells	Medullary carcinoma

Comment

In this series, 14 cases of malignant neoplasm in the liver were successfully diagnosed by punch biopsy. In an additional five cases, negative punch biopsies were followed immediately by open biopsies that yielded positive results. Punch biopsies have a definite value in patients with clinically advanced hepatic neoplasms, especially in cases where general anesthesia is contraindicated. If the punch biopsy is unsuccessful, open biopsy under regional or local anesthesia, if thought necessary, should be performed. Other diffuse liver processes, such as hemochromatosis (and amyloidosis, as proved in later cases) have been successfully diagnosed by the punch-biopsy technique. These conclusions are based primarily on the histological results. The value of the punch biopsy in other liver disease processes not clearly delineated histologically must be assessed by the clinicians.

When questions remain unanswered following a punch biopsy, open biopsy should always be considered. The 10 cases reviewed

in which the diagnosis was misleading or in error should serve as a reminder of the fallibility of this procedure.

The cases reviewed represent a consecutive series of attempted biopsy procedures as evaluated by the pathologists at the University Hospital. All such specimens received in the department of pathology have been included in this series. None were excluded because of size; indeed, one specimen in which there was no recognizable liver tissue was included in the punch series.

It is quite certain that the clinical evaluation of the punch series would alter the statistics considerably in favor of more positive diagnoses. The statistics included here reflect only what can be expected from the pathologist.

In the final analysis, the biopsy method used should be individualized. Clinical and laboratory data should be considered, together with the probability of making a positive diagnosis as weighed against the possibility of attendant complications. It is hoped that this study may serve as a practical guide to the latter considerations.

Summary

In 40 (37.3%) of 107 liver punch biopsies performed at the University of Michigan Hospital covering a five-year period, 1951-1956, a positive histological diagnosis was made.

The punch biopsy appears to be most useful in suspected cases of neoplasm in an enlarged liver or in diffuse pathological processes, such as hemachromatosis.

The efficacy of open biopsy of the liver is well substantiated. The information from gross examination of the liver and other viscera, coupled with adequate liver wedges removed from suspicious areas, permitted a positive histological diagnosis in 169 out of 172 cases (98.3%).

Department of Surgery, University Hospital.

Vascular Syndromes from Dilatation of Arteriovenous Communications of the Sole of the Foot

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In the last few years there has been an increase in knowledge of the arteriovenous communications, described almost simultaneously by Sucquet and Hoyer about 1860.

The anatomists' investigations have been particularly informative, especially those of Vastarini-Cresi, Grosser, Spanner, Clara, and Bucciante. On the basis of these contributions, arteriovenous anastomotic formations are known to be present in many organs and tissues of the body. However, those in the more distal areas of the extremities are better understood. Here they present various anatomic structures, ranging from the more complex neuromuscular arterial glomus of Masson to the simpler direct anastomosis without intermediate channel. The physiology of these shunts is not well known. Generally they are considered to represent a regulating device of the capillary flow. The factors which regulate the partition of the flow between arteriovenous communications and capillary bed are still undefined, even though the object of numerous recent investigations.

Nevertheless, on the basis of physiopathologic knowledge of congenital and traumatic arteriovenous shunts, the pathologic picture of the arteriovenous communications in the lower extremities has been better defined. Piulachs, Vidal-Barraquer, and Biel published in 1952 an interesting report on the role of the arteriovenous communications of the foot in pregnant women with varicosities. In their opinion, the arteriovenous communications (which they improperly considered congenital arteriovenous fistulas) become dilated as the result of hormonal stimulation and produce a dilatation of the corresponding venous tree. Piulachs and Vidal-Barraquer, in 1953, extended this pathogenic concept to other types of varices. In 73% of 53 cases of varicose ulcer, Vogler found dilated arteriovenous communications, localized mostly in the ulcerated area but sometimes diffuse throughout the whole leg. Fontaine and his colleagues, in 1954, were able to demonstrate the presence of dilated arteriovenous communications in 25 patients complaining of primary or postphlebitic varices. In the majority they were located in the ulcerated area and in the sole of the foot. The findings of these authors are mainly based on frequent serial arteriophlebographies and on the presence of an abnormally high oxygen saturation of the venous blood in that area.

Arteriography generally shows a great speed of arterial opacification and a precocious appearance of the venous filling. The small branches from which originates the varicose venous tree present little ampullary dilatations, which the authors just mentioned consider due to the dilated arteriovenous communications. These data, in the light of our knowledge of the arteriovenous fistulas, appear to demonstrate well the existence of direct communications between arteries and veins.

The Arteriovenous Anastomosis in Varices

The arteriographic and clinical study of a large group of patients with primary varices and the postphlebitic syndrome allowed me to confirm most of the observa-

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From the Department of Surgical Pathology, University of Genova.

Fig. 1.—Drawing of the circulation of the leg and foot in a case of varicose syndrome: The main arterial channels are dilated, and the arterial circulation time is increased. The finest branches of the plantar arteries feed directly the venular network through the dilated arteriovenous shunts.

tions mentioned (Figs. 1 and 2). Some cases of postgravid varicose veins which regressed at delivery and increased on occasion of subsequent pregnancies confirm precisely the hypothesis of Piulachs and his associates.[5] In all these cases I was able to find radiologic evidence of the increased speed of the circuit, of the characteristic maculae, and of the precocious venous opacification. It is my impression, though, that the arteriovenous communications are of too small a caliber, even though dilated, to be radiologically visualized (normally their caliber varies from 30μ to 60μ) and that the picture of maculae adjacent to the arteriovenous communications are, rather, the result of dilatation of the postanastomotic venules. My conclusions are also different from those of Piulachs and Vidal-Barraquer in relation to the role of the arteriovenous communications in producing the primary varicose syndrome. First, in many cases it is not possible to demonstrate a dilatation of the arteriovenous communications, and in other cases, which I shall mention later, in which the arteriovenous communications of the sole of the foot are definitely dilated, varices are not found. Furthermore, the study of traumatic and congenital arteriovenous fistulas taught us

Fig. 2.—Serial arteriophlebography in a case of primary varices of the lower limb. The first, third, and fifth studies were done preoperatively, while the second, fourth, and sixth were done after the surgical interruption of the arteriovenous communications in the sole of the foot. In the first x-rays, it is possible to see the quick visualization of the whole arterial tree of the foot, the presence of "maculae" near the shunts, and the precocious visualization of the venous tree. After the operative intervention, it is possible to see that the arterial and venous circulation times are slower and that the "maculae" have disappeared.

that the dilated veins of varicose type enter the venous tree in a retrograde rather than in an anterograde manner. Consequently, the dilatation of the arteriovenous communications of the sole of the foot would not explain the appearance of varices in the leg. I was, therefore, convinced that the dilatation of the arteriovenous communications is secondary to the varicose disease itself and that this dilatation occurs whenever the valves are incompetent and the weight of the column of blood is on the small postcapillary venous branches. I think that the arteriovenous dilatations are not determinant in producing the varices, but represent a secondary phenomenon, aggravating the varicose picture. The increase in blood flow they produce further engorges the varicose tree.

In some cases of the primary varicose syndrome I had to face the problem of eliminating these short circuits before the surgical treatment of the varices. Finding it impossible to close the anastomosis directly, I proposed isolating them from the rest of the arterial tree by interrupting most of the arterial branches which supplied them, taking advantage of the experience acquired in the surgical treatment of many cases of congenital arteriovenous fistulas of the extremities. The efficacy of these interventions has been demonstrated by the evident modification of the local hemodynamic situation. Postoperative arteriography shows a slowed circuit, both arterial and venous, and the disappearance of the macular pattern.

The experience acquired in the field of short blood circuits in arteriovenous fistulas and in the varicose syndrome permitted me to interpret some cases that I was previously unable to understand. As a matter of fact, I often happened to see patients who clinically presented a picture of vascular difficulty of the lower extremities without any vascular alteration as demonstrated by routine arteriographic examination and the common functional and laboratory tests. This is usually the case in young people who, after prolonged walking or dancing, note the appearance of a more or less sudden acute train of events, associated with coldness all over the area of the dorsal or the plantar arterial distribution. The sensation of cold is painful and is accompanied by a deep burning pain. If the patient keeps walking during the crisis, the painful sensation gets worse and spreads from the foot to the ankle, then to the leg, and sometimes up to the thigh. The patient has to stop, but, unlike intermittent claudication, the painful symptoms do not stop immediately with rest, but disappear very slowly. In some cases the sensation of pain and coldness persists for several hours, and sometimes for several days.

Objectively, the skin of these patients is well nourished and pink, but it becomes pale during the crisis. The arterial pulsations are usually well felt, but in some cases the pulsation of the anterior tibial artery is not detectable, and in a few others the pulsation of the posterior tibial artery is hardly palpable.

Arteriographic Findings

It was mainly our improved arteriographic technique, using serial arteriography at short intervals, that allowed me a better knowledge of the local hemodynamic picture in some of my patients. If in these cases the serial arteriography is performed under narcosis at short intervals (Figs. 3 to 6), it is possible to make those observations I have already mentioned in relation to varices. The speed of arterial circulation is enormously increased. In fact, the last arteriolar branches of the foot are seen to opacify within 5 to 6 seconds, instead of in 11 to 14 seconds, as is normal. It is almost constantly possible to see the presence of radiopaque maculae in the sole of the foot. These may be localized in the region of the heel, in the anterior submetatarsal area, or even throughout the sole of the foot. Finally, the venous network appears quite early. In some cases, even after

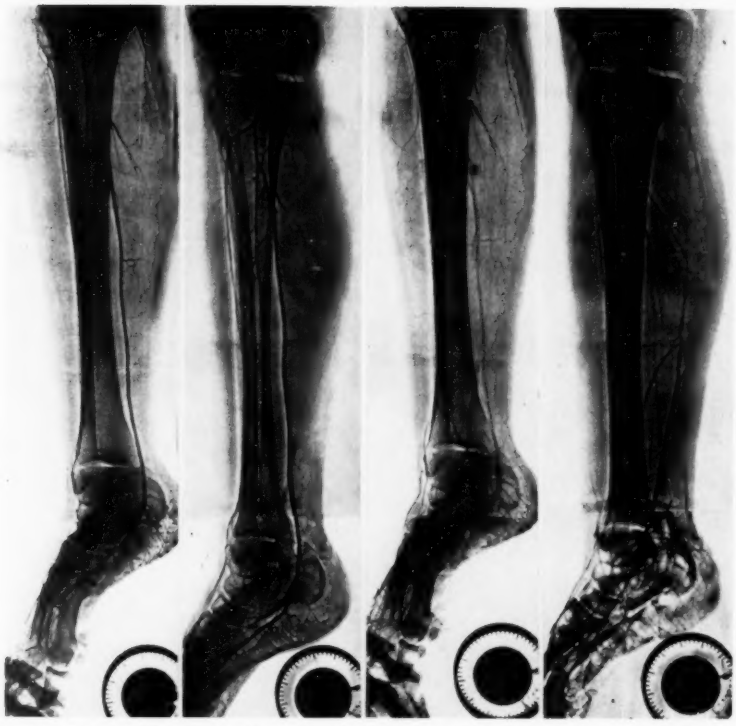


Fig. 3.—Serial arteriography in a case of dilatation of the arteriovenous communications of the right heel. The first and third radiographs were done preoperatively; the second and fourth, postoperatively. Before the operation, the posterior tibial artery is better visualized than the anterior tibial artery; afterward, the two arteries, as well as the venous vessels, are visualized at the same time. Moreover, at the site of the dilated arteriovenous communications, there is an absence of the peculiar "maculae."

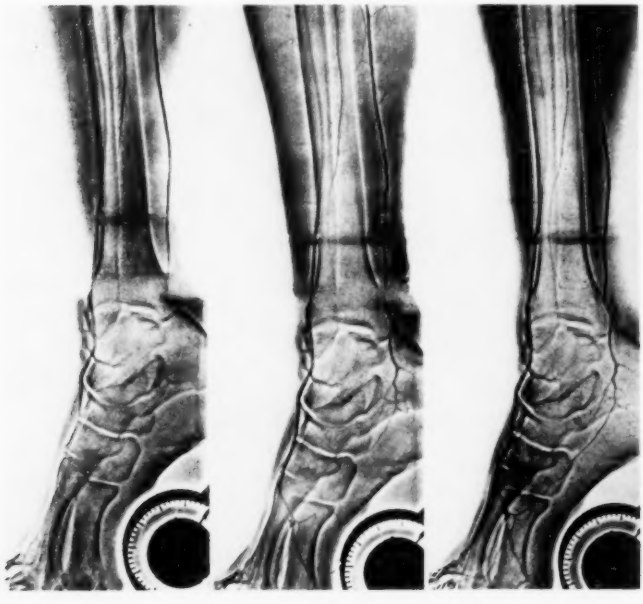


Fig. 4.—Serial arteriography in a case of dilatation of the arteriovenous communications of the forefoot. The good filling of the anterior tibial artery and the dorsal artery of the foot and the delay of opacification of the posterior tibial and plantar arteries are noted.

Fig. 5. — Serial arteriography in the same case as that shown in Figure 4: on the left side the preoperative, and on the right side the postoperative, x-rays. After the surgical intervention the "maculae" of the arteriovenous communications cannot be seen any longer, and the ratio of the blood flow of the anterior tibial artery to that of the posterior tibial artery is modified to the advantage of the latter.

five to six seconds it is possible to see small veins depart from the maculae to join the major branches forming the veins of the foot and then entering the veins of the leg. The superficial and the deep veins of the leg are thus sometimes opacified as well. In the majority of cases there is also demonstrable a difference in opacification of the two main arteries of the leg. More frequently the anterior tibial artery, much reduced in caliber, fills very slowly, and its branches are poorly opacified by the time the venous pattern from the posterior tibial area is well filled up to the middle of the leg. In other cases, on the contrary, the posterior tibial artery fills slowly, and the anterior tibial artery, which is larger, opacifies to the forefoot, supplying the whole plantar arcade, with ramifications to the anterior submetatarsal plantar area where the appearance of the characteristic maculae is noted. In still other cases the two arteries fill at the same time and generally in them the maculae appear over the entire sole of the foot, and the early films show all the veins of the foot and of the leg.

Fig. 6. — Serial arteriography in a case of dilatation of the whole sole of the foot. The tibial arteries are both dilated and lengthened; there are shunts in the whole sole of the foot.

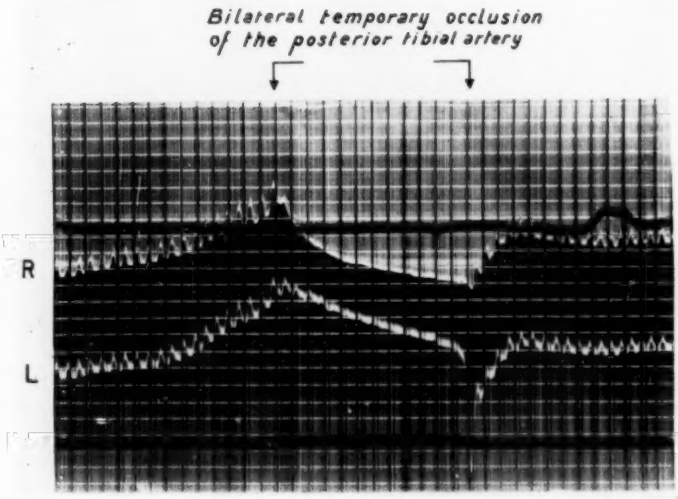
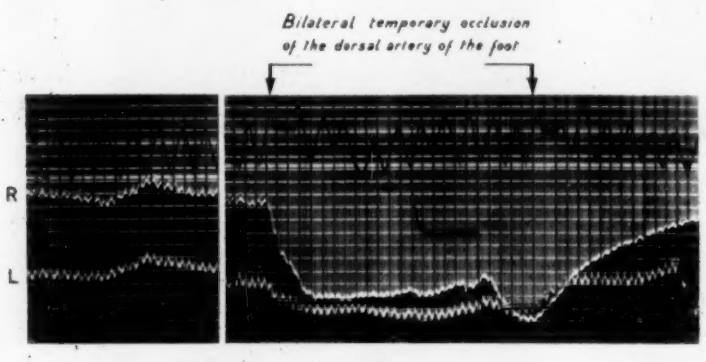


Fig. 7.—Bilateral plethysmography of the first toe in a case of dilatation of the arteriovenous communications of both feet. Compression of the posterior tibial artery in the retromalleolar sulcus abolishes completely the arterial pulse and the blood flow to the first toe. This is further demonstration of a real preponderance of the posterior tibial and plantar arteries in the vascularization of the first toe.

Plethysmographic Findings and O_2 Saturation in the Venous Blood

The plethysmographic investigation usually gives data of remarkable interest. It sometimes shows a picture of ischemia of the toes, and sometimes, on the contrary, a picture of hyperemia. The most interesting observations concern the behavior of the digital flow when the blood supply of one of the two main arteries of the foot is temporarily arrested by pressing on the dorsal artery of the foot, or on the posterior tibial artery in the retromalleolar sulcus (Figs. 7 and 8). If one occludes the artery which is arteriographically dominant in the arteriolization of the toe, a noticeable drop in digital volume and pulse wave is observed, with a return to the former values

Fig. 8.—Plethysmography of the first toe in a case of dilatation of the arteriovenous communications of the right foot: The temporary compression of the dorsal artery of the foot greatly reduces the pulse and the flow of the first toe. This demonstrates that in this case the digital blood flow is principally from the dorsal artery of the foot.



as soon as the pressure is released, whereas compression of the other artery does not substantially modify the situation.

In the great majority of cases there is also demonstrable an increase of oxygen saturation of the venous blood coming from the area of the arteriovenous communications. To substantiate this fact, it is, however, necessary to compare the oxygen content of the arterial blood with the oxygen content of the venous blood coming from the arteriovenous short circuit. Since these short circuits are limited to a small vascular area, the hyperoxygenation of the venous blood is not detectable after it becomes mixed with blood coming from other areas. Since it is not always possible to draw blood from the specific vein involved, in many cases we overcame this difficulty by drawing blood directly from the plantar veins during surgical intervention. In this way, we observed that the blood of the lateral plantar artery and the blood of the homologous vein presented no difference in oxygen saturation. Examining critically the angiographic and clinical data, the existence of an arteriovenous short circuit is evident. As a matter of fact, we find all the characteristic features, such as (*a*) increase, in the basal state, of the speed of the arterial circulation and a quick venous return; (*b*) presence of peculiar radiographic patterns of a macular shape, where there is a transition from the arterial terminations to the first venous roots, patterns which, in my opinion, are an expression of a dilatation of the venous tree into which the anastomosis drains; (*c*) increase of the oxygen saturation in the veins coming from the area where the previously mentioned x-ray patterns are observed; (*d*) dilatation and lengthening of the efferent arteries of the involved vascular area; (*e*) reduction of the blood flow in the territories which are below and in the collateral, or "cognate," areas. These physiopathologic elements are the same as those observed in a short circuit due to congenital or traumatic arteriovenous fistula. As we know, these features are related to the size of the fistula; we may therefore explain their smaller magnitude in the case of the small arteriovenous communications in a limited territory as compared with those related to a large fistula. However, the result is the same. The dilatation of the arteriovenous communications finally brings about an exaggeration of their function, resulting in a direct flow of a major quantity of blood from the arteries to the veins, with reduction of the capillary flow. The dilatation of the arteriovenous communications acts to reduce the peripheral resistance, increasing the frontal pressure and the speed of flow and decreasing the lateral pressure in the afferent artery.

Anatomic Data

Referring these phenomena to the anatomical peculiarity of the arterial circuit of the leg and of the foot, one could postulate certain aspects that this vascular syndrome might assume. In fact, anatomic variations exist in the arterial distribution of the various areas of the sole of the foot (Fig. 9). According to Wachsmuth and Lang, in 55% of cases the posterior tibial artery and its two branches, the lateral plantar and medial plantar arteries, supply the whole sole of the foot. In the remaining 45% of cases, the anterior tibial artery supplies the whole forefoot, the plantar arcade being supplied by one or two perforating transmetatarsal arteries, which are branches of the dorsal artery of the foot. In these cases usually there is an anastomosis between the plantar arcade and the lateral plantar artery, but this anastomosis sometimes may not exist. These anatomical data suggest that in over 50% of cases the plantar supply is due to the posterior tibial artery, whereas in the other cases the forefoot is supplied by the anterior tibial artery and the posterior portion by the posterior tibial artery. We can thus explain how various clinical pictures may exist, depending on the site of the dilated arteriovenous communications. As a matter of fact, if in a plantar area corresponding to one of the

Fig. 9.—In the drawings are shown the more frequent modes of arterial circulation of the sole of the foot. In the first drawing, the plantar arch is formed by the metatarsal perforating arteries, branches of the dorsal artery of the foot. In this case there is no anastomosis with the plantar arteries. In the second drawing, the plantar arteries and the metatarsal perforating arteries, which come from the dorsal artery, contribute equally to form the plantar arcade. In the third, the plantar arcade is from the dorsal artery, whereas in the fourth the whole arterial plantar net is formed by the plantar arteries.

two main arteries of the leg some dilated arteriovenous communications exist, there is the possibility that the other artery will be subject to the consequences of the blood division and will lose part of its flow.

Arterial Syndromes Due to Dysfunction of the Plantar Arteriovenous Anastomosis

Three syndromes have been observed relating the clinical picture with the radiologic findings.

First Syndrome.—The arteriovenous communications of the sole of the foot are supplied only by the plantar arteries, branches of the posterior tibial artery. Their pathologic dilatation produces, because of their increased caliber and their number, the phenomena due to a large communication between the arterial and the venous system: more speed of arterial circulation, increased arterial flow, and quick filling of the veins coming from the arteriovenous communications. Clinically these phenomena produce a remarkable reduction of blood flow in the "cognate" arteries supplied by the anterior tibial and peroneal arteries, with reduction of the speed of the circulation and consequent reduction of the temperature of the corresponding area. The syndrome may become acute whenever an exaggerated stimulation, such as a prolonged march, further increases the dilatation of the arteriovenous communications. The deprived arteries become spastic and produce local ischemia. On the other hand, overworking arteriovenous communications give a burning sensation on the sole of the foot. This feeling is intense because of the rich innervation of the arteriovenous communications,

TABLE 1.—*Symptomatology in Three Syndromes of Dilated Arteriovenous Anastomosis of the Sole of the Foot*

Symptoms	Arteriovenous Anastomosis		
	Anterior (4 Cases)	Posterior (9 Cases)	Diffuse (14 Cases)
Pain of forefoot	4	1	3
Pain in entire sole of foot	0	5	5
Pain ascending to leg	1	2	3
Paresthesia and burning of foot	2	1	3
Pain in calf	0	1	5
Hypothermia of forefoot	2	1	3
Hypothermia of entire foot	2	1	4
Redness of toes	1	0	0
Cyanosis of forefoot	2	0	0
Cyanosis of the foot	0	2	3
Malleolar edema	1	2	2

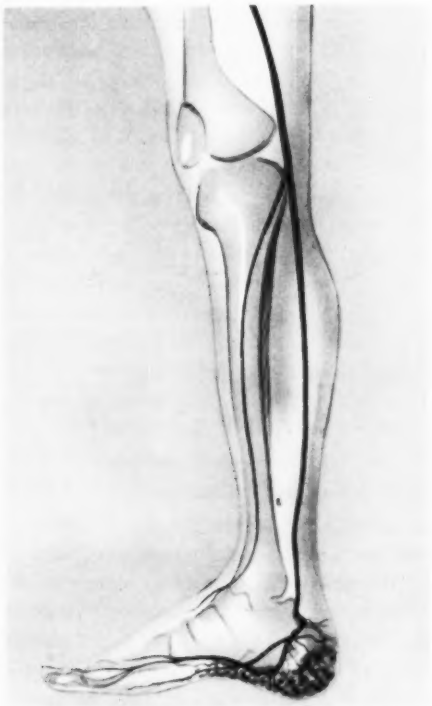


Fig. 10.—Drawing of the arterial circulation of the leg and foot in the syndrome of dilatation of the arteriovenous communications of the heel. The posterior tibial artery and the plantar arteries are dilated, and the speed of their flow is greater than in the anterior tibial artery and in the dorsal artery of the foot, which seem thin.

and also because of the capillary ischemia consequent to the massive arteriovenous shunt. In nine cases it was possible to demonstrate this phenomenon. The symptoms vary in their intensity and extent, depending upon the number of the arteriovenous communications (Table 1).

In some cases the arteriovenous communications of the heel alone are dilated, and the phenomenon of ischemia is very intense in the forefoot (Fig. 10). In other cases the arteriovenous communications of the whole sole of the foot are dilated, and therefore the phenomena are more intense in the area of the tibial artery and over the foot.

Second Syndrome.—The arteriovenous communications in the distal half of the sole of the foot are supplied by intermetatarsal perforating arteries, coming from the anterior tibial artery (Fig. 11). When just the arteriovenous communications of this area are dilated, a syndrome the opposite of the one just described is observed. The shunt is from the anterior tibial artery, while the posterior tibial artery fills slowly and is smaller than normal. The ischemic crisis then involves mainly the posterior plantar area, but it may also affect the toes. The painful burning sensation is felt in the anterior part of the foot, and the pain sometimes radiates during the crisis, as in the first syndrome. We have observed five cases of this sort.

Fig. 11.—Drawing of the arterial circulation of the leg and foot in the syndrome of dilatation of the arteriovenous communications of the anterior plantar segment. The anterior tibial artery, the dorsal artery of the foot, and the perforating transmetatarsal arteries, tributary arteries of the shunts, are dilated, and their blood flow is faster than in the posterior tibial and plantar arteries, which seem to be very small.

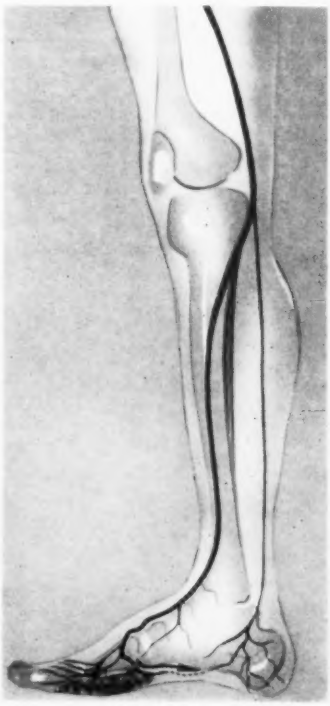


Fig. 12.—Drawing of the arterial circulation in a case of dilatation of the arteriovenous communications of the whole sole of the foot. The anterior tibial and the posterior tibial artery both participate in the shunt; so the circulation time is faster in both the arteries.

Third Syndrome.—The anatomic situation is the same as in the second syndrome. The anterior tibial artery supplies the anterior part of the foot, but the arteriovenous communications are dilated in the entire sole of the foot, including those depending upon the posterior tibial artery (Figs. 12 to 16). The symptoms of arteriovenous shunt involve the areas supplied by both arteries, and on arteriographic study both vessels are seen to opacify at the same time. The reduction of the speed of the blood flow occurs especially in the collaterals of the two main arteries of the leg. This explains the frequent presence of pain in the calf during walking, while the burning sensation involves the whole foot, associated with coldness from capillary ischemia. We have observed 14 cases of this sort.

From a general point of view, we can say that the most constant and typical symptomatology is observed in the dilatation of the arteriovenous communications supplied by the anterior tibial artery alone, and this is explained by the constant localization of the short circuits in the forefoot. When the dilated arteriovenous communications are supplied by the two arteries, the blood flow of the foot is increased to a maximum and the ischemia phenomena involve mainly the muscular arteries of the leg. It is understandable, then, how the symptomatology might vary and be dependent upon the vascular situation and, therefore, be correctly interpreted only on the basis of the angiographic examination.

Fig. 13.—Outline of the operation for dilatation of the arteriovenous communications of the heel; surgical interruption of the arterial branches tributary to the shunts.

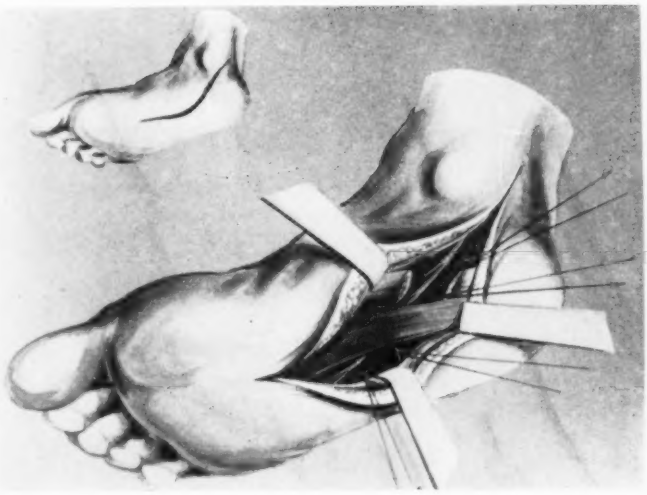


Fig. 14. — Surgical intervention to tie the afferent arteries of the arteriovenous communications of the heel. Incision is made from the interior retromalleolar sulcus down to the foot sole. Once the calcaneal channel is opened by cutting the adductor hallucis muscle, it is possible to dissect out a segment of the flexor digitorum sublimis. When this muscle is mobilized, it is possible to see the lateral plantar vascular and nerve bundle, which is just under the muscle. All the arterial branches to the heel are divided and ligated as they arise from the posterior tibial artery and the beginning of the lateral plantar artery.

Therapy

The therapy of the dilatation syndromes of the arteriovenous communications might, theoretically, involve the use of drugs acting specifically on this particular segment of the vascular tree, at least in the early stages. The experimental investigations of the action of various drugs on the function of the arteriovenous communications, however, thus far have not given definite results. In a few cases we have used a mixture of the methanesulfonates of three ergot alkaloids: dihydroergocornine, dihydroergocristine, and dihydroergokryptine (Hydergine) and atropine, with little success.

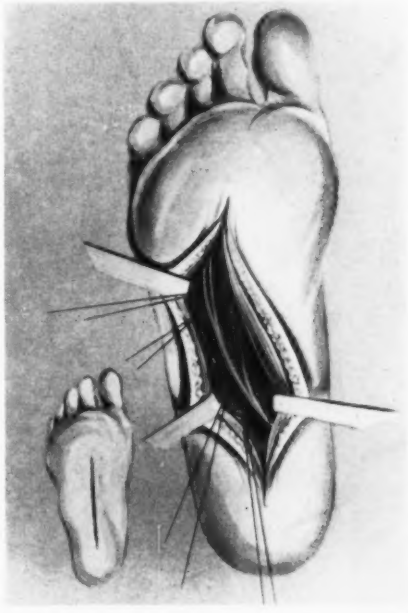
Our interest has been directed mainly toward the possibility of interrupting surgically the short circuits. Since the direct surgical elimination of the arteriovenous anastomosis seems impossible, we have tried to isolate them from the rest of the arterial tree by interrupting as many afferent arterial branches as possible (Fig. 13).

On the basis of this principle, I have perfected three types of intervention which are adapted to the three syndromes.

Interruption of the Afferent Arteries in the Medial and Posterior Part of the Heel.

A curved incision is made below the medial malleolus (Fig. 14). The terminal part of the posterior tibial artery and the beginning of the lateral plantar artery are isolated below the calcaneal ligament, which is interrupted. All the branches going in a plantar and posterior direction toward the

Fig. 15.—Surgical intervention for dilatation of the arteriovenous communications of the whole sole of the foot. Lateral paramedian incision. Through the fibers of the plantar aponeurosis and the flexor digitorum sublimis muscle, it is possible to visualize the plantar lateral artery and tie its collateral branches.



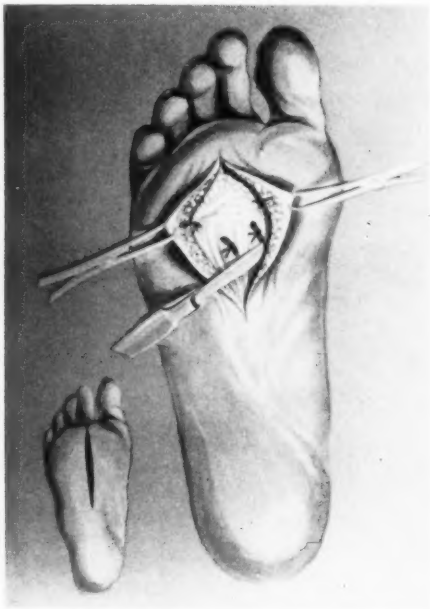


Fig. 16.—Surgical intervention for dilatation of the arteriovenous communications of the forefoot. Incision is made in the middle of the anterior plantar tract. Dissection of the adipose tissue from the aponeurosis and division of the arterial branches which go to the shunt through the plantar aponeurosis are accomplished.

skin are divided between ligatures. The operation may be enlarged by extending the incision further on the sole of the foot in the midline. The abductor hallucis is interrupted so as to expose the calcaneal sulcus. In the midline an interspace through the plantar muscle is developed so that the artery can be dissected free and followed down to the middle of the foot. The branches to the skin are interrupted.

Interruption of the Arterial Afferents of the Arteriovenous Communications of the Lateral Part of the Sole of the Foot.—An external paramedial longitudinal incision on the sole of the foot is made starting from the heel and extending down to the metatarsal area (Fig. 15). Dissection through the fibers of the aponeurosis and of the plantar muscle and isolation of the lateral plantar artery are accomplished. The lateral branches leading to the skin are divided.

Interruption of the Arterial Afferents of the Arteriovenous Communications of the Sole in the Metatarsal Area.—A longitudinal midline incision on the sole in the metatarsal area is made (Fig. 16). The subcutaneous fat is dissected free from the plantar aponeurosis all over the metatarsal area, and the small perforating arteries of the aponeurosis are ligated.

Present Surgical Procedure

After the first cases, an effort was made to simplify the surgical methods by interrupting the plantar arterial branches where they are superficial to the plantar aponeurosis. This may be accomplished with a technique similar to the one described for the second syndrome, that is, by dissecting the adipose plantar pillow from the plantar aponeurosis in the areas where the dilated arteriovenous communications have been identified. Here the numerous arterial and venous branches are cauterized, or, if of larger caliber, ligated. The plantar incisions used at first were in the midline, but since delayed healing occurred in some cases as the result of a little area of marginal necrosis and in others with primary healing there was some delay in firm union, I have recently used an incision on the lateral side of the foot. Much faster recovery has been observed (Fig. 17). A number of cases may be considered completely recov-

TABLE 2.—*Results of Surgical Treatment of Dilated Arteriovenous Anastomosis of the Sole of the Foot*

	Cases	Recovered	Very Much Improved	Stationary	Uncontrolled
Diffuse arteriovenous anastomosis	13	2	6	4	1
Posterior arteriovenous anastomosis	9	1	7	1	—
Anterior arteriovenous anastomosis	5	2	2	—	1
	27	5	15	5	2

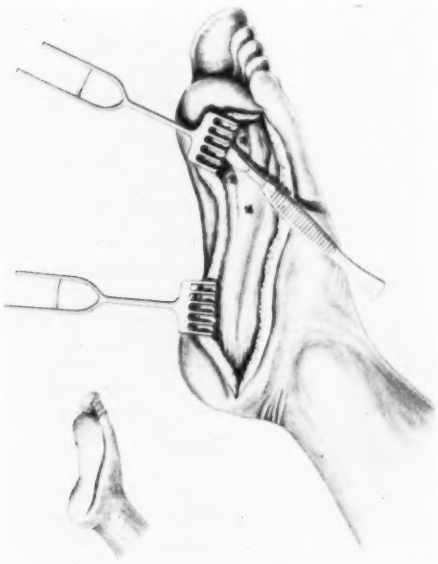


Fig. 17.—Lateral approach to dissect the skin and the adipose tissue of the sole of the foot from the plantar aponeurosis.

ered, with disappearance of all difficulty. Many cases have been considerably improved, having disappearance of most of the disturbances and persistence of only some isolated symptoms. Only a few cases had no significant improvement. These results may be considered a further confirmation of the pathogenic interpretation presented.

Summary

The clinical aspects of some functional circulatory syndromes of the leg and foot due to the dilatation of the arteriovenous anastomosis of the sole of the foot are illustrated. The arteriographic and plethysmographic findings are also presented. From the observed data I have concluded that the dilatation of the arteriovenous communications in an area of the sole of the foot is the cause of a shunt of blood that damages the contiguous vascular areas, which become ischemic. A satisfactory method of surgical management is described.

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Failure of Equine Arterial Heterografts Treated by Controlled Peptic Proteolysis

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Arteries from animal sources are readily available which possess physical properties similar to those of human arteries. If chemical or antigenic modification allowed their successful use in man, the difficulties attending the procurement of adequate numbers of normal human arteries for use as grafts would be alleviated. This study is concerned with methods of changing the antigens of equine arterial tissue by partial peptic digestion and the immune response in the dog and man following implantation of equine carotid arteries modified by partial proteolysis. Experiences with these grafts in 16 subjects and the immunologic reactions produced in them form the basis of this report.

Previous Work

A method of altering the antigens of the equine arterial wall has been previously described.[1] Three-hour digestions of filtrates of horse carotid artery homogenates with a suspension of 0.1% crystalline pepsin in acid buffer at 37 C was found to abolish complement fixation in a test system using rabbit antiserum to the filtrates. Digestion of intact artery segments at 5 C for six days and then two hours at 37 C, followed by homogenization and filtration, produced a filtrate which also failed to react with the antiserum. However, it was found that digestion for longer than 48 hours at 5 C, followed by two hours at 37 C, weakened the response of the arterial wall to intraluminal pressure: Distensibility was increased at higher pressures. Segments of equine carotid arteries digested short of this limit, frozen, and sterilized with cathode radiation proved quite successful as replacements for 4-5 cm. segments of canine abdominal aortae. Ten partially digested heterografts served as satisfactory conduits for blood flow for as long as 15 months. On the other hand, 8 of 10 undigested equine carotid arterial segments implanted similarly failed as canine abdominal aortic grafts. Five ruptured or thrombosed within one month, and three developed aneurysms.

On the basis of results in canine recipients, partially digested equine carotid arteries were frozen, sterilized, and used as femoral artery bypass grafts in 16 patients critically in need of peripheral blood flow improvement. Results are summarized in Table 1.

TABLE 1.—*Fate of Partially Digested Equine Arteries After Implantation for Femoral Occlusive Disease*

Case No.	Method of Digestion of Heterograft: Time Hr.	Temp.	Time Graft Functioned	Cause of Failure
1	2	37 C	0	Immediate thrombosis
2	3	37 C	0	Same
3	27	5 C+		
	1½	37 C	0	Same
4	27	5 C+	0	Same
	1½	37 C		
5	3	37 C	0	Same
6	3	37 C	0	Same
7	36	5 C+		
	2	37 C	3 mo.	Late thrombosis
8	48	5 C+		
	1½	37 C	6 mo.	Late thrombosis
9	3	37 C	6 mo.	Multiple aneurysms
10	3	37 C	7 mo.	Same
11	4	37 C	2 mo.	Same
12	27	5 C+		
	1½	37 C	10 mo.	Same
13	36	5 C+		
	2	37 C	18 mo.	Same
14	36	5 C+		
	2	37 C	3 wk.	Same
15	48	5 C+		
	1½	37 C	2 mo.	Same
16	48	5 C+		Same
	1½	37 C	26 mo.	and thrombosis

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Results

Clinical Results.—Six of the grafts failed because of early thrombosis. Pulses in the grafts could not be demonstrated 24 hours after operation. Thromboses in these cases were attributable to extensive arteriosclerosis of the host arterial tree in most instances. Postoperatively, the 10 remaining patients developed bounding grafts, peripheral arterial pulsations, and dramatic improvement in peripheral blood flow. During the first 24 hours after operation, the graft usually increased in diameter approximately two times and lengthened sufficiently to have a sigmoid course along the medial aspect of the thigh. The postoperative course of most of the remaining patients was uncomplicated; their wounds healed well, and they were discharged with functioning grafts. The exception was Case 14. A small subcutaneous hematoma developed about the graft on the 14th postoperative day; massive hemorrhage occurred 24 hours later. The bleeding point was found at the base of a small arterial branch of the graft; it was closed with silk. Three days later another hemorrhage prompted removal of the graft. Multiple small saccular aneurysms were present in the diffusely dilated graft.

Pulsation of the graft in Case 7 could not be felt three months after discharge, and the graft is presumed to have thrombosed. However, in this patient a gangrenous ulcer of the great toe subsequently healed, and intervention to reestablish blood flow has not been required. Another person also developed late graft thrombosis without requiring amputation or reoperation because of impaired blood flow.

Eight of the ten patients with initially successful grafts have required excision of the graft because of aneurysm formation. The postoperative interval required for the development of the saccular dilatation has varied from 3 weeks to 26 months.

Pathological Results.—All excised grafts removed showed multiple saccular aneurysms (Fig. 1). With one exception, the aneurysmal process involved the entire length of the graft. The heterograft removed in Case 12 had two areas of aneurysmal dilatation separated by a 15 cm. graft segment of normal diameter. The portion of the wall representing the original graft was extensively infiltrated with lipid deposits.

Microscopic examination of the eight excised grafts showed that the aneurysm walls were composed of fibrous tissue without remnants of the original heterograft. The progression of events could be traced in the grafts of varying ages. Essentially, the picture was one of rapid dissolution of the

Fig. 1.—Heterograft removed from the leg in Case 16 after functioning for 26 months.

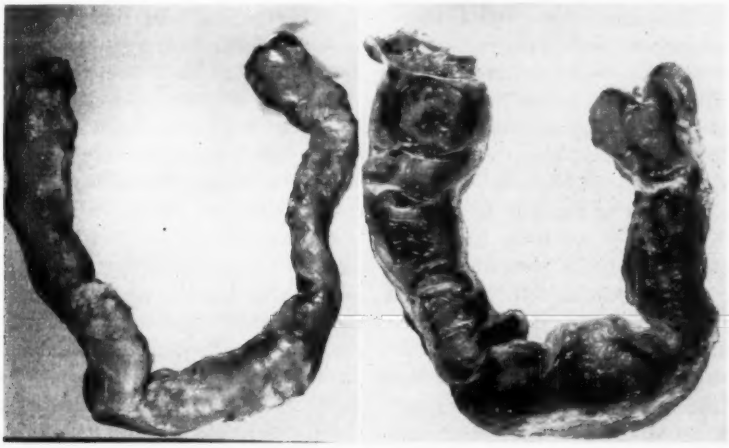

Fig. 2.—Photomicrograph of the wall of a digested equine carotid artery after sterilization and reconstitution before implantation. The intima has been digested away. Verhoeff-Van Gieson elastic tissue stain; × 104.

heterograft associated with chronic inflammatory cellular reaction. The grafts at the time of implantation showed pale-staining nuclei and loss of the intima but preservation of the elastic tissue framework (Fig. 2). The specimen removed three weeks after implantation (Case 14) was acellular and showed partial loss of the reticular arrangement of the elastic tissue (Fig. 3). At two months the excised grafts showed fragmentation of elastic tissue and chronic inflammatory reaction on both intimal and adventitial surfaces (Fig. 4). Plasma cells, eosinophils, and histiocytes were prominent in the cellular infiltrate at this stage. Elastic tissue was absent except for occasional fragments in the grafts implanted six months or longer. Invasion of the remnant of the graft by host collagenous tissue could be demonstrated in the specimens removed at 10, 18, and 26 months (Fig. 5).

Immunologic Reactions.—Reactions of the sera from patients having heterograft implantation are shown in Table 2. To obtain heterophile titers, reactions of the sera with a saline suspension of sheep red cells containing added bovine serum albumin were recorded, and the reaction was repeated after adsorption of the serum with a 20% guinea pig kidney extract for 20 minutes at room temperature.[2] The adsorbed sera were also tested for horse red

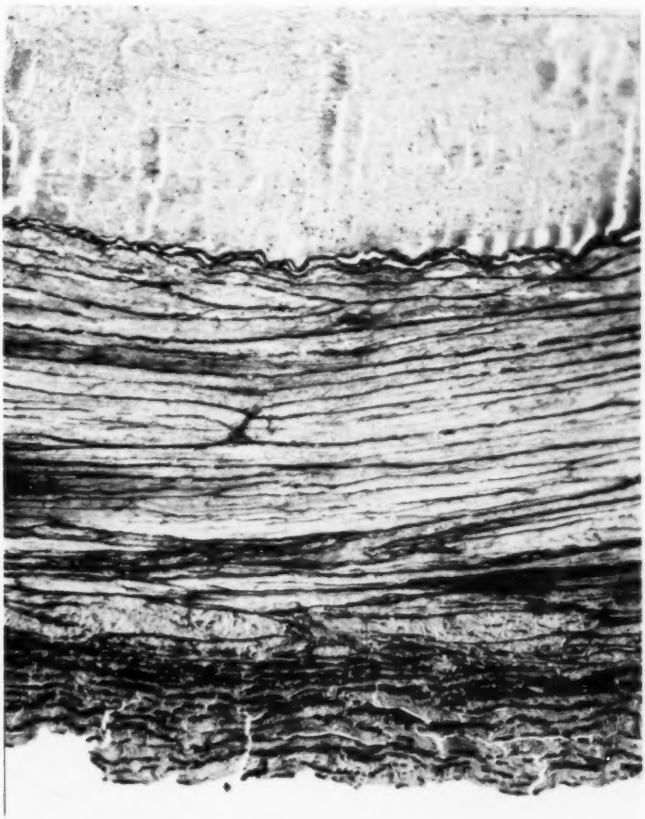

Fig. 3.—Section from the wall of the heterograft removed in Case 14 three weeks after implantation. The intimal surface here is covered with fibrinous thrombus. Verhoeff-Van Gieson elastic tissue stain; × 104.

cell-agglutination activity. The complement fixation of each serum was measured in a standard complement-fixation system using varying amounts of saline extract of horse carotid arteries which had been dialyzed and analyzed for nitrogen content. There was infrequent complement-fixation activity and inconstant sheep cell agglutination. Horse red cell agglutination, however, was present in high titer in almost all sera.

Attempts to demonstrate precipitable antibody were unsuccessful both in the sera and in eluates of the excised grafts. Sera adsorbed with guinea pig kidney extract and then with sheep red cells failed to show hemagglutination in a test system of tanned sheep red cells which had been exposed to a saline extract of horse carotid artery.[1] In other words, we have not been able to demonstrate specific circulating antibody of the ordinary variety. Tests for cellular antibody were performed in three patients after removal of dilated heterografts (Cases 9, 10, and 15). Neither skin-patch tests with horse carotid artery homogenate nor intradermal injections of saline extract of homogenate containing 10μg. of protein nitrogen produced any reaction in these patients.

Sera from dogs having either partially digested or untreated equine arteries implanted gave the reactions shown in Table 3.

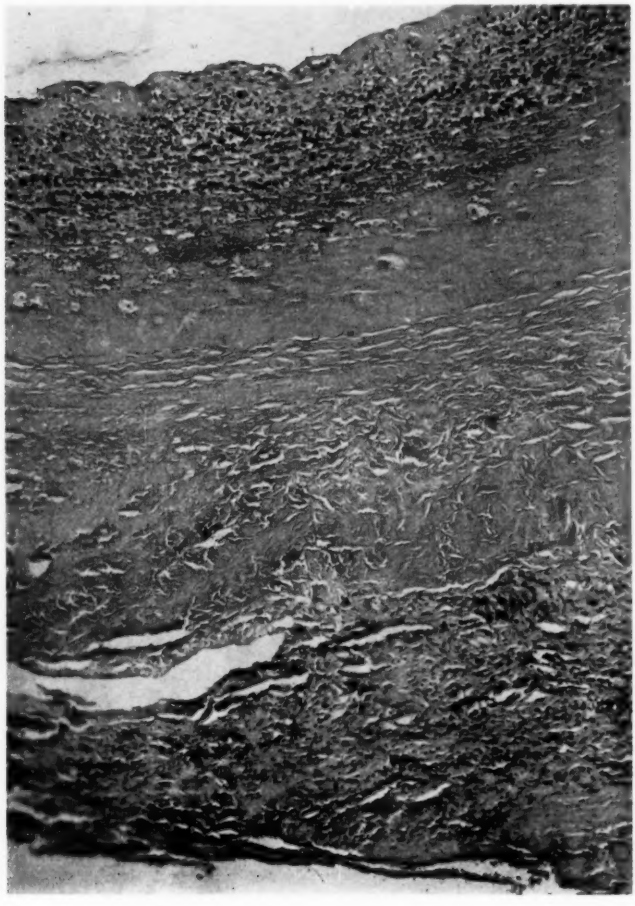

Fig. 4. — Heterograft from Case 11, showing both intimal and adventitial inflammatory reaction around the acellular graft remnant. Hematoxylin and eosin; × 77.

These differed from the human sera reactions only in that Forssman reactivity was almost absent. A series of rabbits immunized with soluble and insoluble extracts of both digested and undigested horse arteries showed the same type of reactions as did the human sera. These reactions could not be definitely correlated with the development of aneurysm.

Comment

Why the graft walls were weakened enough to allow aneurysm formation cannot be determined with surety. Digestion of important structural elements in the arterial wall might be cited. However, those grafts subjected to the most digestion seemed to function as long as those receiving minimal digestion. One of the grafts in this series, Case 16, subjected to the most prolonged peptic digestion at 5 C, did not develop aneurysm until 26 months after implantation. Indeed, this digestion might well have prolonged the appearance of aneurysm in this patient. Three of the five heterografts subjected to some digestion at 5 C functioned longer without aneurysm formation than did any digested at 37 C. The suggestion that peptic digestion delayed aneurysm formation in some equine arterial heterografts used in man and the fact that partial peptic digestion of the short arterial

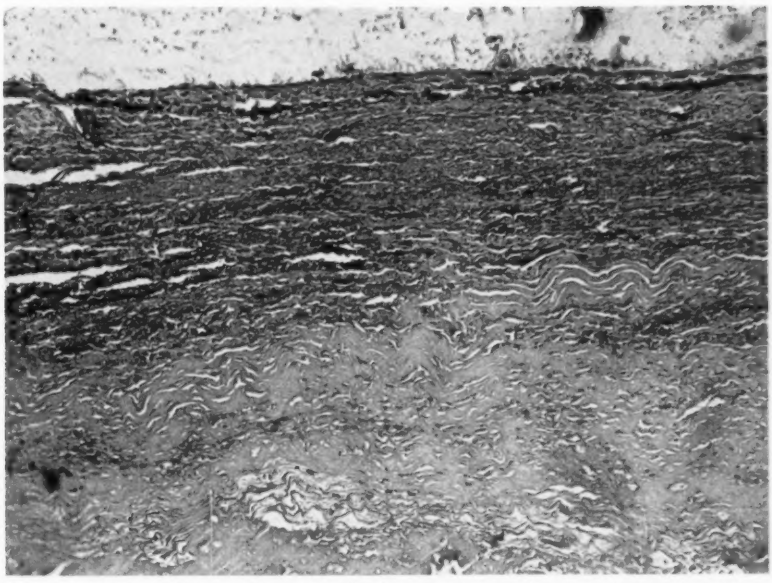

Fig. 5.—Invasion of the graft remnant by host collagenous tissue in microsections from the heterograft removed after 26 months of function in Case 16. Hematoxylin and eosin; × 90.

TABLE 2.—*Reactions of Sera from Patients with Equine Artery Heterografts Implanted*

Case No.	Graft Status	Time After Implantation, Mo.	Reciprocal Sheep RBC Agglutination Titer	Reciprocal Heterophile Titer	Reciprocal Horse RBC Agglutination Titer	Complement Fixation in Presence of	
						NHE *	PHE *
1	Thrombosed	¼	0	0	0	0	0
2	Thrombosed	5½	20	0	640	0	0
6	Thrombosed	¼	0	0	0	0	0
	Thrombosed	5	0	0	128	0	0
7	Thrombosed	4¼	0	0	0	0	0
	Thrombosed	6½	0	0	640	--	--
8	Thrombosed	1¾	224	28	448	0	0
9	Thrombosed	2½	0	0	32	0	0
	Thrombosed	5¾	0	0	32	--	--
	Aneurysm	6	0	0	0	--	--
	Removed	8	0	0	28	--	--
10	Patent	⅛	0	0	32	1+	2+
	Aneurysm	7	160	--	320	0	0
11	Patent	¼	0	0	0	0	0
	Aneurysm	¾	112	14	112	3+	1+
	Removed	5¾	0	0	40	0	0
12	Patent	2½	80	--	640	3+	2+
13	Patent	3	0	0	640	0	0
14	Early aneurysm	½	112	56	256	3+	2+
	Removed	4	0	0	80	--	--
15	Aneurysm	2	56	14	256	3+	2+
	Removed	3	112	0	256	0	0
16	Patent	3⅛	20	0	320	0	0
	Patent	7½	20	0	640	0	0

* NHE = saline extract of normal fresh horse carotid artery.
* PHE = saline extract of pepsin-digested horse carotid artery. Both extracts were dialyzed and adjusted to contain 10 μg. of total nitrogen in the first-strength tube. The number of plus signs (+) indicates number of two-fold antigen dilutions showing fixation.

TABLE 3.—*Reactions of Sera from Dogs with Equine Artery Heterografts Implanted*

Dog No.	Duration Implantation	Reciprocal Sheep RBC Agglutination Titer	Reciprocal Heterophile Titer	Reciprocal Horse Red Blood Cell Agglutination Titer
A. Undigested Heterografts				
36	4 mo.	0	0	896
94	4 mo.	14	28	1792
26	5½ mo.	28	0	224
3844	7 mo.	56	0	224
B. Digested Heterografts				
100	3 mo.	14	0	—
96	4 mo.	0	0	—
73	5 mo.	0	0	448
10929	7 mo.	28	0	—
8	12 mo.	56	0	112

heterografts implanted into dogs definitely reduced the incidence of their suture-line rupture, thrombosis, and aneurysmal dilatation indicate at least a partially beneficial effect of controlled peptic digestion upon heterograft survival.

All patients who received equine artery transplants showed some indication of immune response. Intensity of reaction in the systems tested seemed to have little relation to the rate of aneurysm formation. It might seem that the successful results in dogs was related to the lack of Forssman reaction in these animals. Similar lack of serum activity in the unsuccessful group of undigested heterografts does not obviate this possibility. Dogs contain Forssman antigen in their tissues and would not be expected to develop Forssman antibody.

Thus, the possibility exists that rejection of equine heterografts can be caused by reaction to either of two antigens. If one were a Forssman substance and the other a material destroyed by pepsin, the results in man and dog would be easily interpreted. It would appear that the evaluation of heterografts for use in man would best be made experimentally in a species capable of Forssman reaction, such as the pig. Similarly, bovine heterografts might be more successful in man than equine grafts, for bovine tissue lacks significant Forssman antigen. Of course, response to Forssman substances cannot be primarily responsible for the success or failure of human arterial homotransplantation, since only tissues from persons of blood group A can be shown to contain these substances. Nevertheless, reactions to homografts suggestive of immune response are frequently seen. The reactions to some homografts are similar to the reaction seen about heterografts; degeneration and aneurysm formation in arterial homotransplants are observed, particularly after long periods of implantation.[4]

Partial peptic digestion of horse arteries does not suit them for use in man. Some combination of lipid extraction and proteolysis eventually may be found which will alter animal arteries sufficiently to allow their use in human beings. At present, the lack of a suitable assay technique makes a systematic study of this problem impractical.

Summary

Equine carotid arteries modified by partial peptic digestion were used as femoral bypass grafts in 16 persons. Of these grafts, six were immediate failures, two later became occluded, and eight were excised because of multiple saccular aneurysms. The longest functional survival was 26 months.

The dissolution of the heterograft observed microscopically was greater the longer the period of implantation.

Sera of patients with equine heterografts were studied for evidence of immune response. No specific precipitable antibody was demonstrated. However, several sera showed significant Forssman antibody, and almost all sera had high titer of horse red cell agglutinins.

It is concluded that partial peptic digestion of horse arteries does not suit them for use in man. It is suggested that experimental evaluation of heterografts for use in man be done in a species lacking Forssman tissue antigens rather than in the dog.

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Experimental Artery Graft Angulation

A Comparison Study with Dacron Collapsible Tubing, Tapp-Edwards Crimped Nylon Prosthesis, and Freeze-Dried Preserved Artery Homograft

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The development of collapsible and noncollapsible synthetic cloth prostheses, suitable for replacing segments of the arterial tree, has led us to investigate their use in conditions that favor angulation and kinking of the graft. We have selected for comparison study (*a*) a collapsible prosthesis, (*b*) a flexible prosthesis, and (*c*) a preserved artery homograft. As this problem of graft angulation has been afforded little emphasis with respect to the selectivity of some of the newer cloth prostheses, this study is presented to emphasize the importance of graft flexibility in order to delineate further the criteria in selecting the proper artery substitute.

Method of Study

Adult mongrel dogs were used. Intravenous pentobarbital (Nembutal) anesthesia and sterile technique were employed for each operation. Through separate incisions, the common iliac artery and femoral artery were isolated. The former was divided approximately 2 cm. below the aortic bifurcation; the latter, 3 cm. distal to the inguinal ligament. In addition, a tunnel was formed in the subcutaneous tissue of the groin, cephalad to the inguinal ligament, through which the graft was inserted.

Three different types of artery graft substitutes were employed: (*a*) freeze-dried preserved artery homografts; (*b*) seamless, collapsible Dacron tubing, and (*c*) Tapp-Edwards crimped nylon prosthesis. In each instance the diameter of the graft was isodimensional only in respect to the common iliac artery.

The proximal iliac artery anastomosis was created in an end-to-end fashion, after which the graft was threaded through the subcutaneous tunnel in the iliofemoral area and anastomosed to the femoral artery in an end-to-side fashion. Two continuous sutures of 00000 arterial silk were employed for each anastomosis. Once arterial continuity and blood flow were established, the abdominal and leg incisions were closed, and the animals were transported to an x-ray table, where arteriography was performed, 20 cc. of 50% diatrizoate (Hypaque) being employed as the contrast medium. Two arteriograms were made on each animal—the first with the operative leg in an extended position, the second with the leg flexed and abducted to between 45 and 60 degrees at the hip joint. A total of 15 dogs was employed, 5 for each type of graft.

Results

The results of this experiment are portrayed in the arteriograms shown in *A*, *B*, and *C* of the Figure. In each instance, when a Dacron-collapsible prosthesis was employed, roentgenographic evidences of angulation occurred when the leg was in the flexed position. This finding was observed on two of the five occasions on which a preserved artery homograft was used; in the remaining three cases tortuosity of the graft, rather than true angulation, was noted. In no instance did a Tapp-Edwards crimped nylon prosthesis display evidence of angulation.

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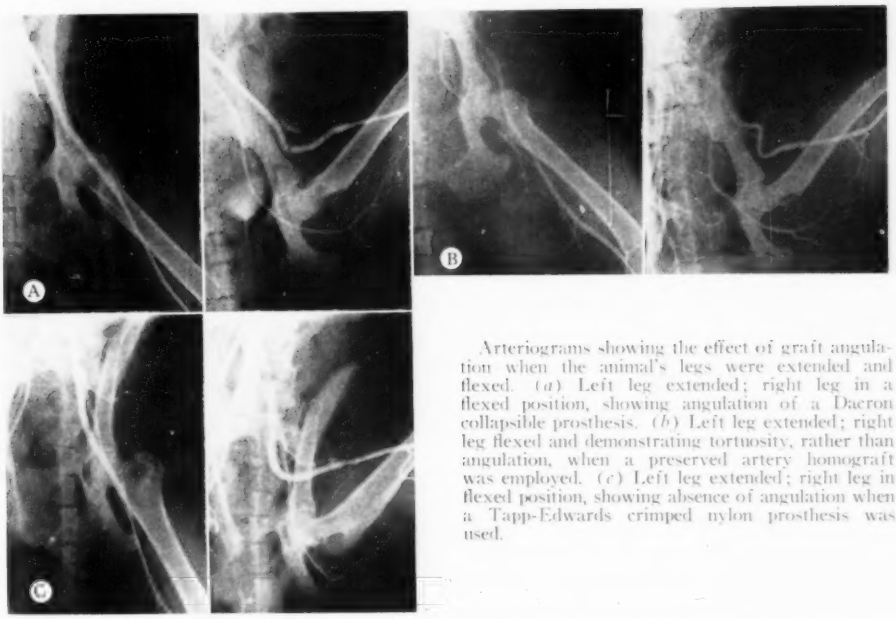

Arteriograms showing the effect of graft angulation when the animal's legs were extended and flexed. (*a*) Left leg extended; right leg in a flexed position, showing angulation of a Dacron collapsible prosthesis. (*b*) Left leg extended; right leg flexed and demonstrating tortuosity, rather than angulation, when a preserved artery homograft was employed. (*c*) Left leg extended; right leg in flexed position, showing absence of angulation when a Tapp-Edwards crimped nylon prosthesis was used.

Comment

The basic criteria required of fabric materials for use as artery substitutes have been established by the experimental studies of Hufnagel,[5] Deterling,[1] and others. However, the anatomical position of the artery graft with respect to its angulation has received but little attention in the design of some of the presently available commercial cloth prostheses.

In the past, Hufnagel[5] was one of the first to realize this problem of graft angulation when a fabric prosthesis was employed to bridge a flexion crease. Later, Tapp and Edwards[2] showed that a crimped cloth prosthesis did not kink when subjected to extreme degrees of flexion. With the recent introduction of more satisfactory materials, such as Dacron and Teflon, in the form of cloth prostheses, this problem of graft angulation assumes greater importance. Furthermore, owing to the nature of various arteries amenable to artery-grafting procedures, angulation may be expected to occur when a collapsible type of prosthesis is used to replace the iliofemoral, popliteal, and axillary arteries.

To emphasize this problem further, our radiographic studies demonstrated the disturbance to the normal pattern of blood flow that occurs when a collapsible cloth prosthesis is subjected to angulation. It seems reasonable to assume that such a condition favors thrombosis of the graft, and introduces abnormal structural stresses and strains to the graft per se, and consequently an inefficient flow system results. Distinctly different, however, is the radiographic appearance of the flow pattern when a crimped cloth prosthesis is subjected to similar experimental conditions. In each instance a smooth, uninterrupted flow pattern through the graft was noted. Significant, too, is the observation that tortuosity, rather than angulation, occurred in two instances when flexion was introduced to the limb that contained a preserved artery homograft, suggesting that this type of artery substitute may still serve a useful purpose when properly employed.

At present, the advantages of certain cloth prostheses are apparent[3,4]; however, other factors, besides their basic material specificity, must be recognized in the clinical ap-

plication. In this regard, our experimental studies indicate that a collapsible cloth prosthesis is not to be recommended as a means of establishing arterial continuity in situations where angulation may occur. Suffice it to say that the ideal artery graft has yet to be discovered, and, as such, compromises have to be made in selecting the prosthesis most suitable for the condition at hand.

Summary

This study was designed primarily to emphasize the problem of graft angulation when a cloth prosthesis was used to bridge a flexion crease. In each instance, when a collapsible cloth prosthesis was subjected to in vivo angulation, radiographic evidence of interference with the normal blood-flow pattern was noted. However, a crimped flexible prosthesis did not manifest this phenomenon when it was subjected to similar experimental conditions. As considerable emphasis has been afforded to the material specificity of cloth prosthesis, our study indicates that the flexibility of the graft is a requisite if it is to be employed in areas where angulation of the graft may occur. At present, the Tapp-Edwards crimped nylon prosthesis fulfills this specific requirement.

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Surgical Care in Post-Traumatic Renal Failure

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The presence of crushed, necrotic, and infected tissues in a patient with acute renal failure can enormously complicate the management of the patient's hospital course and, in many cases, can lead to a much more rapid progression of uremia and potassium intoxication. This situation has been abundantly documented in recent years.[1-3] While it is generally agreed that necrotic tissue should be immediately debrided in these patients,[4,5] it has been noted that at times little benefit seems to accrue from this procedure.[4] The following cases are offered as examples of what may be expected of surgery under various circumstances in post-traumatic acute renal failure.

Clinical Material

These patients were treated at a specialized treatment center in Korea where casualties who developed post-traumatic renal insufficiency were referred. An artificial kidney was employed as an adjunct in controlling uremia and potassium intoxication. Many of these patients had received massive wounds. Many of them exhibited large areas of nonviable tissue which it had not been possible to remove in the initial surgery at forward hospitals. The medical regimen used in the therapy of these patients has been presented in considerable detail elsewhere.[3,5] In the following presentations the term oliguria is used to indicate a urinary output of less than 500 cc. a day. The term diuresis indicates a rise in the urinary output above 1000 cc. a day following a period of oliguria. The case histories are presented in three groups.

Group 1: Patients with acute renal failure uncomplicated by any accompanying tissue damage or infection

Group 2: Patients with acute renal failure complicated by the presence of massive tissue necrosis and/or infection in whom the infected necrotic tissue could not be adequately removed

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TABLE 1.—*Admission Data; Renal Insufficiency* *

		Vital Signs					Laboratory Studies					
	Age, Yr.	Time After Reaction or Injury, Hr.	B. P., Mm/Hg	Pulse Rate	Resp. Rate	Temp. (F)	Na mEq/L.	K mEq/L.	Cl mEq/L.	CO_2 mEq/L.	NPN Mg.%	Hct. Mm.
Group I												
A	20	48	120/70	74	18	99.6	128	3.8	91.2	23.5	88.6	29
B	22	48	106/70	100	..	97.0	128	6.1	89.6	..	203	14
Group II												
A	20	48	84/60	120	52	100.8	137	6.6	92.5	21.6	87	..
B	21	48	120/70	88	..	99.6	125	6.1	88	27	88.2	40
C	21	72	150/90	125	28	99.6	129	7.5	88	28	191	42
D	21	48	120/70	110	20	..	128	7.3	79.5	..	174	27
Group III												
A	22	72	120/90	110	32	101.5	113	6.2	82	21	144	30
B	23	48	170/105	90	16	..	116	6.6	88	21.9	163	30

* The table summarizes the major data observed on the admissions of these patients to the Renal Insufficiency Center. As can be seen, the electrolyte pattern was often considerably distorted, with relatively high serum concentration of potassium and NPN, although only 47 to 72 hours had elapsed since initial injury.

TABLE 2.—*Potassium and Nonprotein Nitrogen Removed by Dialysis* *

Case	Dialysis, No.	K, mEq. Removed	NPN, Gm. Removed
I B	1	No data	55
IIA	1	80	11
	2	50	90
	3	120	74.7
Total		250	175.7
IID	1	90	35.0
	2	160	26.0
	3	130	25.5
	4	110	63.0
	5	20	72.0
	6	190	30.0
Total		700	251.5
IIIA	1	300	86

* The table is a summary of the available data on the total amounts of serum potassium and nonprotein nitrogen removed from the patient at each hemodialysis and the total for all hemodialyses on each patient. Unfortunately, such data were not available for all the patients. Patient IB had renal failure subsequent to a transfusion reaction; Patient IIA had renal failure associated with severe peritonitis, and Patient IID had massive injury of soft tissue associated with renal failure. Patient IIIA had bilateral gas gangrene of both lower extremities with marked electrolyte problems prior to amputation and hemodialysis.

Group 3: Patients with acute renal failure associated with massive necrosis of tissue and/or infection in whom the infected and necrotic tissue was removed adequately

For the sake of brevity, vital signs and laboratory studies obtained on admission are listed together in Table 1. Table 2 summarizes the available data on the amounts of potassium and nonprotein nitrogen removed from the patients by dialysis.

Group I

Patients with acute renal failure uncomplicated by accompanying tissue damage or infection.

CASE A.—This patient developed a hemolytic transfusion reaction during secondary closure of some superficial soft-tissue wounds. Oliguria developed, with an output of only 100 cc. of urine in the first 24 hours after reaction, and the patient was transferred to the Renal Insufficiency Center.* He did well on medical therapy. No hemodialysis was required, and diuresis began on the eighth postreaction day. Serum potassium never rose above 5 mEq/L. Nonprotein nitrogen rose gradually, reaching a maximum of 273 mg. % on the 9th postreaction day, falling thereafter to normal on the 16th day.

CASE B.—This patient had a severe transfusion reaction when he received a pint of mismatched blood. After 48 hours of oliguria, he was transferred to the R. I. C. He was treated initially by medical measures, but, on the fourth postreaction day, symptoms of nausea, vomiting, and disorientation made clinical management difficult. Hemodialysis was used to ameliorate these symptoms. He responded well to hemodialysis and to subsequent medical management, and, after 18 days of oliguria, diuresis was finally established. He was evacuated in good condition and with a normal serum NPN on the 30th postreaction day. It is interesting to note that, except for a brief period prior to the first dialysis when the potassium rose to 6.3 mEq/L., the serum potassium during the patient's protracted oliguria never rose above the normal range. The NPN reached a maximum of 273 mg. % on the 16th postreaction day.

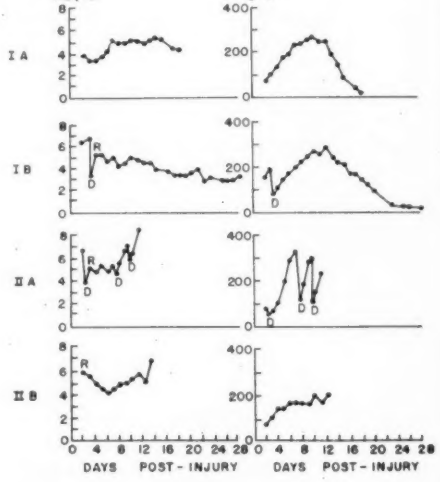

Chart 1.—Daily changes in the serum concentrations of potassium and NPN. Patients *IA* and *IB* had renal failure without concomitant tissue injury or infection, and daily changes in serum potassium and NPN were of relatively small magnitude, and the amount of change each day remained about the same. Patient *IIA* had severe peritonitis associated with his renal failure, and changes in serum potassium and NPN concentration were of large magnitude, with marked increases despite repeated hemodialysis. Patient *IIB* did well at first, but developed a large pelvic abscess with a concomitant terminal rise in serum potassium and NPN concentration, despite the fact that he was past the stage of oliguria and had developed diuresis.

* Hereafter referred to as the R. I. C.

Comment.—These two cases are presented to serve as a contrast to the following cases, in which severe infection and trauma were an important part of the clinical picture. As the data in Chart 1 illustrate, the accumulation of nonprotein nitrogen and potassium in the serum of these patients was a slow progression, with a small and fairly stable increment being added each day, as compared with the very rapid changes found in the serum of those patients in whom renal failure was accompanied by marked amounts of infection and trauma.

Group II

Patients with acute renal failure, complicated by the presence of massive tissue necrosis and infection, in whom the infected and necrotic tissue could not be removed.

CASE A.—This patient sustained a bullet wound in the epigastrium, with much loss of tissue from the abdominal wall, transection of the transverse colon, and a large laceration in the right lobe of the liver. During the first 24 hours after operation, the blood pressure remained at shock levels, despite transfusions of 5500 cc. of blood, 850 cc. of plasma, and 200 cc. of albumin. Urine output on the first postinjury day was 200 cc., and the patient was transferred to the R. I. C. 36 hours after operation.

On admission he appeared critically ill, with flushed face, mental confusion, and shallow, rapid respirations. The heart and lungs were normal. A portion of the exteriorized colon was black and necrotic. The abdomen was silent. The ECG showed evidence of moderate potassium intoxication. The colostomy was opened and the necrotic bowel debrided. Because plasma potassium had reached a level of 6.6 mEq/L., with ECG changes only 36 hours after operation, dialysis was undertaken, chiefly to reduce his hyperkalemia. Immediately after dialysis, 60 gm. of cation exchange resin† was given by rectum.

As indicated in Chart 1, plasma NPN rose rapidly over the next three days. Paralleling this change, the patient's clinical condition deteriorated, with development of disorientation and a uremic frost. Dialyses on the sixth and ninth postinjury days were followed by brief clinical improvement and an abrupt relapse. Following the third dialysis, plasma potassium rose 2.7 mEq/L., and the NPN rose 117 mg. % in less than 24 hours. Daily urine output gradually increased to a maximum of 425 cc. on the ninth postinjury day. On the 10th postwound day the patient's blood pressure became unobtainable, and he died. Serum potassium taken eight hours before death was 8.6 mEq/L.

At autopsy an extensive, generalized peritonitis was found, with 100 cc. of purulent exudate lying free in the pelvis. No perforation of the bowel was found except in the exteriorized segment. There was a 6 cm. laceration of the right lobe of the liver, surrounded by some fibrin. The kidneys each showed a large purple medulla with some thickening of the cortex. They weighed 250 gm. each.

Comment.—In this patient renal failure was complicated by severe and uncontrolled peritonitis. Despite repeated hemodialysis, uremia could not be controlled, and the patient died.

CASE B.—This patient was injured by a land mine and reached a Mobile Army Surgical Hospital (M. A. S. H.) three hours after injury. Blood pressure was unobtainable, and resuscitation required 5000 cc. of whole blood. At surgery, a left above-the-knee amputation, right orchiectomy, and extensive debridement of a large avulsed area of skin and muscle over the right anterior thigh, measuring 18×18 cm., were carried out. Wounds of the right buttock and right arm were also debrided. A compound, comminuted fracture of the right radius was treated with splints. On the first postinjury day, urine output was only 200 cc. Early on the second postinjury day a water-load test produced no diuresis, and the patient was transferred to the R. I. C. for treatment.

The patient responded well to medical management, and diuresis began on the sixth postinjury day. The patient continued to do well until the 10th postinjury day, when his rectal temperature rose to 102.8 F and increasing lethargy was noted. All dressings were changed, and the wounds were found to be relatively clean, although draining profusely. On the 11th and 12th days his general condition deteriorated and he became disoriented. Despite an output of 4000 cc. of urine on the 11th day, his serum potassium increased slowly to 6.0 mEq/L., and his NPN reached 205 mg. %. On the 13th day some foul drainage appeared on the long-arm cast. The cast was removed, revealing a large abscess in an inadequately debrided wound tract, which extended from the right wrist to the elbow. This abscess was opened widely, and 300 cc. of foul pus was removed. Cultures grew Aerobacter aerogenes and Staphylococcus aureus. The patient showed little improvement following the procedure, and in the afternoon of the 13th day he suddenly and rather unexpectedly died.

†SKF Special Resin No. 648—a cross-linked polyacrylic ammonium carboxylate cation exchange resin. This material was provided by Smith, Kline & French Laboratories, Philadelphia.

Plasma potassium that morning was 7.1 mEq/L. None of his wounds showed much evidence of granulation or other signs of healing.

At autopsy it was found that one of the perforating wounds of the buttock communicated with a compound fracture of the tip of the sacrum and a perirectal abscess, which filled the pelvis and extended to the peritoneal floor. The bowel was intact. Muscles of the right forearm were soft, friable, and purple-red. The brachial artery was thrombosed at the level of the midhumerus. There was marked cerebral edema. Renal congestion was noted.

Comment.—This patient did well at first and was apparently recovering from his renal failure, having passed into the diuretic phase. The sudden deterioration of his clinical state appears to be associated with the progression of his pelvic abscess and the necrosis of muscle in his arm. A rising serum potassium, despite a urine output of 4000 cc. per day, is most unusual. As a general rule the serum potassium does not rise until the urinary output is depressed below 500 cc. per day.[6]

CASE C.—This patient was wounded by mortar fire, sustaining comminuted fractures of the right tibia, fibula, and femur and multiple large, penetrating soft-tissue wounds of both legs, the left buttock, and the right flank, with extensive muscle damage. In the course of debridement at an M. A. S. H. two hours after injury, the patient's blood pressure became unobtainable, and surgery was discontinued. A total of 14,000 cc. of blood, 500 cc. of plasma, and 200 cc. of albumin was given on the day of injury, followed by 2500 cc. of blood on the second postinjury day. Urinary output totaled only 200 cc. in the first 48 hours after injury. The patient was therefore transferred to the R. I. C.

On admission he was acutely ill but oriented. Massive destruction of the musculature of both legs and the left buttock was noted. The right lower leg and foot were cold. The ECG showed characteristic evidence of potassium intoxication. Serum potassium was 7.6 mEq/L. Dialysis by means of the artificial kidney was begun within four hours of admission. Following this the patient seemed much improved. Six hours after the dialysis a right below-the-knee amputation, with extensive debridement of both legs anteriorly and posteriorly, was done. The wound of the right flank was explored, and the right kidney was found to be lacerated. It was left in place, and the renal bed was drained. In spite of oral resin therapy, potassium intoxication recurred, with a serum K of 7.1 mEq/L. within 48 hours. NPN rose to 163 mg. %.

A second dialysis improved the patient's clinical condition considerably, but 36 hours later, on the eighth postinjury day, potassium intoxication had recurred and the patient developed a silent, tender, distended abdomen and jaundice. Bile peritonitis was suspected, and an exploratory laparotomy seemed necessary. A third dialysis was undertaken in preparation for surgery, but was interrupted by the development of cardiac arrest. The chest was opened, and cardiac massage was carried out. Cardiac function resumed after 15 minutes of massage. The blood pressure rose to 180/70 as dialysis was continued, and serial ECG's showed disappearance of potassium intoxication. Although regular heart action continued, the patient's blood pressure began to fall after the first hour. Repeated small transfusions were of temporary benefit only. Dialysis was continued for six hours. The patient was returned to the ward in poor condition and died early on the ninth postinjury day.

At autopsy a major portion of the posterior muscle groups of both thighs and the left calf were seen to be absent. Despite the extensive debridement, much necrotic muscle remained. No evidence of wound healing was present. Both kidneys were enlarged, with a combined weight of more than 500 gm.; the right kidney contained a laceration 6 cm. long and was surrounded by a large hematoma.

Comment.—Vigorous attempts were made in this patient to remove all necrotic and infected tissue. This could not be done, however, and his potassium intoxication and uremia advanced quite rapidly and were poorly controlled by dialysis.

CASE D.—This patient was wounded by mortar fire, sustaining a traumatic amputation of the left upper thigh at the hip, multiple penetrating wounds of both buttocks and of the lumbar region, and avulsion of most of the skin and much muscle tissue over the left buttock.

Operation, nine hours after injury, revealed a comminuted fracture of the lower sacrum, with multiple perforations of the rectum. The bladder was intact. There was a compound, comminuted fracture of the right fibula. A double-barreled sigmoid colostomy was performed, and the wounds were debrided. During the operation the patient's blood pressure was unobtainable for 45 minutes. It finally rose to 86/40. The patient received a total of 8000 cc. of whole blood on the day of operation. On the first postinjury day the urinary output was only 200 cc., and the patient was transferred to the R. I. C. on the second postinjury day.

On admission it was noted that the wounds of the buttock contained much foul-smelling, necrotic tissue. ECG findings of widening QRS complexes

and high-peaked T-waves indicated marked potassium intoxication. The patient was given hypertonic sodium chloride and dextrose-insulin infusions. Plasma potassium fell from 7.5 to 6.8 mEq/L. This was followed by hemodialysis, which reduced the plasma potassium to 5.1 mEq/L. and the NPN to 97.8 mg. %. Sixty grams of cation exchange resin was given orally. At this time bowel sounds were present and active. The patient took oral feedings well and proceeded to do so throughout the course of his illness. During the next 12 hours (third postinjury day) the plasma potassium rose 2.5 mEq/L., to a level of 7.6 mEq/L., again with marked, characteristic ECG changes. A second dialysis reduced the serum potassium to 4.0 mEq/L. Soon after dialysis, debridement of the large avulsed areas was begun.

The entire left gluteus maximus, most of the gluteus medius and gluteus minimus, and the remaining hamstring muscles were black and necrotic. There was no evidence of gas in the tissue planes, and it was felt that this extensive gangrene of muscle was due to blast effect. All of the involved muscle groups were resected as thoroughly as possible, exposing portions of the ilium and the posterior portion of the capsule of the hip joint. The lower third of the sacrum was found to be partially avulsed, exposing the retrorectal space. A large wound of the right buttock was also debrided. After operation, another 60 gm. of cation exchange resin was given orally.

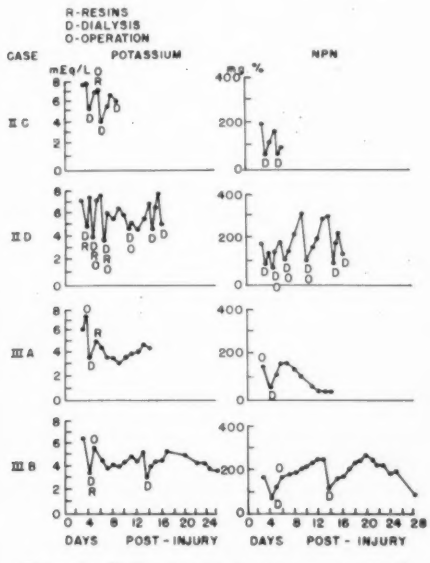

Chart 2.—Daily changes in serum concentrations of potassium and NPN. Patients *IIC* and *IID* had massive tissue injury accompanying their renal failure. Necrotic tissue could not be adequately debrided. Despite repeated hemodialyses, potassium and NPN concentration repeatedly returned to high levels in the serum. Both patients *IIIA* and *IIIB* had relatively high and rapidly rising levels of serum potassium and NPN, but, after surgery, in which all necrotic and infected tissue could be removed, the serum levels of these substances stabilized and could be controlled fairly well.

As indicated in Chart 2, the plasma concentration of potassium and NPN continued to be remarkably labile. Despite a second and third debridement on the 5th and 12th postinjury days, respectively, all of the necrotic tissue could not be removed. Dialysis was repeated on the 6th, 11th, and 14th postinjury days, with relief in each instance of disorientation, stupor, and nausea, with subsequent relapse in 24 to 72 hours. During the 14th postinjury day the plasma potassium rose from 4.7 to 7.1 mEq/L., or 3.1 mEq/L. in a 24-hour period. In the same interval the NPN rose 144 mg. %. The patient became semicomatose, and his blood pressure became unstable. Emergency treatment with hypertonic saline, dextrose, and insulin lowered the plasma potassium to 7.4 mEq/L.; following this, the sixth dialysis lowered the plasma potassium to 5.1 mEq/L. and the NPN to 131 mg. %. However, despite digitalization, nasal oxygen, small amounts of whole blood, 20 cc. of adrenal cortical extract and arterenol, the patient's blood pressure was labile and at times unobtainable during and after the dialysis.

After dialysis the blood pressure continued at very low levels, despite all supportive measures, and the patient died six hours after dialysis, on the 16th postinjury day. The maximum daily urine volume never exceeded 400 cc.

At autopsy it was estimated that two-thirds of the skin over the left buttock and one-third of the skin over the right buttock was missing. The remaining muscle of the buttocks was soft, hemorrhagic, and necrotic in many places. The muscles and retroperitoneal tissue of the pelvic floor showed extensive destruction and necrosis. Sinus tracts communicated through the shattered sacrum and coccyx with the perirectal space. Little or no granulation tissue was present. The right kidney weighed 165 gm., and the left kidney weighed 190 gm.

Comment.—Because of the location of the patient's wounds, repeated debridement did not eliminate large areas of necrotic and infected tissue. Despite a total of six hemodialyses, serum potassium and nonprotein nitrogen levels returned rapidly to high levels after each procedure.

Group III

Patients with acute renal failure associated with severe necrosis of tissue or infection in

whom the infection or necrosis were removed.

CASE A.—This patient was injured by a land mine, sustaining extensive lacerating wounds of both legs, with compound, comminuted fractures of both tibiae and fibulae. At an M. A. S. H., one and one-half hours after injury, he was thought to be moribund, and the blood pressure and pulse were unobtainable. In the first 24 hours after being wounded the patient received 6500 cc. of blood, but his blood pressure remained at hypotensive levels for 12 hours. At operation his wounds were debrided, and a long leg cast was applied bilaterally. During the first postinjury day the patient's urinary output was 980 cc., but studies done by a research unit attached to the M. A. S. H. showed a marked reduction of renal clearance. On the second postinjury day the patient became delirious and violent. His temperature rose to 103 F rectally. Renal clearances were further reduced, and total urinary output for the day was only 320 cc. Because of the progressive depression of renal function, the patient was transferred to the R. I. C. At the time of evacuation, it was noted that the left foot was cold, and it was thought that amputation might be necessary.

On admission at the R. I. C. the patient was semicomatose. Both legs were found to be severely mangled to the knee, markedly necrotic, and extensively gangrenous. Subcutaneous emphysema was present. Cultures were taken, which later showed Clostridium welchii. ECG showed changes indicative of moderate potassium intoxication. In the presence of advanced bilateral gas gangrene, it was felt that immediate operation was indicated. Because of the patient's elevated plasma potassium and lowered plasma sodium, emergency therapy in the form of intravenous hypertonic saline, dextrose, and insulin was given. However, an ECG following this therapy showed an increased in potassium effect, with widening of the QRS complexes and increased peaking of the T-waves. Hemodialysis on another patient was in progress at this time, and we saw no alternative but to proceed with immediate operation.

A bilateral above-the-knee amputation was performed by two teams, working simultaneously. The patient returned to the ward in very poor condition. Immediately after operation his temperature rose to 107.5 F rectally and remained between 105 and 107 despite iced alcohol baths and rectal acetylsalicylic acid. He was completely comatose and without reflexes. The pupils were dilated and did not respond to light. Respirations were Cheyne-Stokes and gasping in character. The ECG showed a rapid progression of potassium intoxication. The pulse was 150 per minute; the blood pressure, 96/62. An arrhythmia on the basis of ectopic auricular foci developed. Another infusion of saline, dextrose, and insulin was given. Despite this, the serum potassium continued to rise to 7.4 mEq/L., an increase of 1.2 mEq/L. in eight hours. Dialysis was started as soon as the artificial kidney was available for use. After two hours of dialysis, during which small amounts of blood were given, the blood pressure was 116/70, and the patient responded briefly to vocal stimuli. At the end of the six-hour dialysis, the blood pressure was 160/80, and the patient was fully conscious and talking, although still somewhat disoriented. The NPN had fallen from 144 to 53.4 mg. % with the removal of 86 gm. of nonprotein nitrogen. Plasma potassium had dropped from 7.4 to 3.6 mEq/L. with the removal of 300 mEq. The temperature was 102 F rectally; respirations were 24 and regular; the patient was returned to the ward in good condition and given 60 gm. of cation exchange resin by rectum. The remainder of the patient's course was uneventful. Diuresis started on the seventh postinjury day. NPN rose to a peak of 168 mg. % on the eighth postinjury day and fell rapidly thereafter. The plasma potassium remained under good control, never rising above normal levels after the dialysis. The amputation stumps remained clean, and granulation tissue began to appear on the 10th postinjury day. The patient was evacuated on the 16th postinjury day.

Comment.—The myositis and gangrene associated with clostridial infection in this patient appeared to lead to a very rapid progression of the uremic syndrome. However, bilateral amputation of the patient's legs successfully removed all areas of infection and necrosis, and, following a single dialysis, the course of uremia was relatively slow.

CASE B.—This patient was wounded by mortar fire. At an M. A. S. H. three hours after injury, penetrating wounds of both knees and thighs were debrided, and an anastomotic repair of the transected left femoral and left popliteal arteries was performed. Before and during the operation the patient receivd 4500 cc. of blood. After operation the left foot was cold and mottled, and survival of the extremity was considered unlikely. On the first postinjury day the urine output was 480 cc. On the second day urine volume was only 150 cc.; therefore the patient was evacuated to the R. I. C.

On admission the patient was fairly well oriented, though he was hiccuping and nauseated; the left foot and lower leg to the level of the midcalf was cold and mottled; the left dorsalis pedis and popliteal pulses were absent. The ECG showed changes indicative of early potassium intoxication. Although the patient's chemical state did not constitute an emergency, a dialysis was decided upon as the quickest method by which to return his high

potassium and lowered sodium to normal, stop his vomiting, and render his course more manageable.

Dialysis was carried out for five hours on the third postinjury day. Serum sodium rose to 141 mEq/L.; potassium fell to 3.9 mEq/L., and NPN fell to 71 mg. %. On the fourth postinjury day the patient was much improved and no longer nauseated. Thirty grams of cation exchange resin was given by mouth. On the fifth postinjury day, only 24 hours after dialysis, the serum potassium was found to have risen 1.9 mEq/L., to a level of 5.8 mEq/L., despite resin therapy. NPN had risen to 124 mg. %. The left lower leg remained cold and mottled to the midcalf, although no definite line of demarcation was in evidence. Because of the rapidly rising potassium and NPN, immediate amputation was deemed advisable, without waiting for further demarcation.

At operation a below-the-knee approach was first attempted, but it was found that all muscles of the posterior compartment of the leg were necrotic, and supracondylar amputation was done. The patient withstood the procedure well. More cation exchange resins were given by rectum, and by the following day the serum potassium had fallen to 4.8 mEq/L. Thereafter the potassium and NPN rose only in small increments. By the 13th postinjury day the NPN was 253 mg. % and the serum potassium 5.6 mEq/L. The patient was drowsy and confused and vomited frequently. In order to control these symptoms, another dialysis was performed. Potassium was reduced to 3.2 mEq/L. and NPN to 120 mg. %. The patient's clinical condition became much improved. Diuresis began on the 18th postinjury day, after which plasma NPN gradually fell to normal levels. The amputation stump and other wounds remained clean, but there were few signs of healing until about the 18th or 19th day, when granulation tissue appeared and began rapidly to fill in the wounds. The patient was evacuated in good condition.

Comment.—Following an initial dialysis in this patient, there was a rapid rise in serum potassium and NPN. Prompt amputation of a gangrenous extremity appeared to slow the progression of uremia considerably.

General Comment

The cases presented in Group II well illustrate the difficulties which assail the clinician in treating patients with acute renal failure when large amounts of infected and/or necrotic tissue are present and cannot be, or are not, adequately removed. In tissues severely injured, whether by infection or trauma, there appears to be a failure of the normal homeostasis, and there is an outpouring of potassium and nitrogen, as well as other intracellular constituents, into the extracellular fluid.[2,7,8] In the patient unable to excrete these substances, there follows a rapid rise in serum NPN and potassium, and these changes are superimposed on serious inbalances already present due to renal failure [9] and post-traumatic electrolyte shifts.[10] When infection cannot be controlled (Case IIA), or when dead and dying tissue cannot be fairly completely debrided (Cases IIC and IID), deterioration is progressive. Perhaps the most striking example of this is in Case IIB. The patient underwent repeated debridement, but, after each procedure, necrotic tissue remained. A total of 700 mEq. of potassium, approximately 18% of the normal body stores, was removed through repeated hemodialysis, but the rapid evolution of potassium intoxication was only temporarily affected. Balch et al.[4] have noted this problem and associated it especially with acute traumatic myositis. In our experience a sufficient degree of infection or necrosis of any tissue in association with renal failure may lead to this syndrome. The course of Patient IIA, who had severe peritonitis, with little tissue trauma, was not unlike the course of Patient IID, who had massive tissue necrosis.

Meroney [11] has pointed out that uremia-like symptoms may be produced by sepsis, and that these symptoms do not benefit by dialysis. It should be emphasized, however, that the presence of severe sepsis need not rule out the possibility that dialysis may benefit the patient. Case IID presents a good illustration of this point in that, despite a low NPN and a substantial amount of sepsis early in the patient's course, hemodialysis at this time was of considerable benefit.

The cases in Group III demonstrate that when all necrotic and infected tissue can be removed in patients with renal failure, the course of the illness may be favorably altered and patients may be salvaged, despite severe initial injury. Basic surgical principles must be vigorously and energetically applied.

When an area of infected or injured tissue is suspected by the appearance of the earliest symptoms or signs, drainage or debridement should promptly be performed. Application of this principle would dictate removal of all doubtful tissue in the course of debridement, rather than following a "wait and see" policy, despite the temptation to be less radical in a patient who is critically ill. This applies also to patients who have lost the blood supply to a limb and in whom a line of demarcation is sought prior to amputation. With normal kidney function, the products of decomposition of ischemic tissues are excreted rapidly without clinical sign of change in the plasma electrolytes, and in such patients waiting for demarcation is justifiable. In the oliguric patient, under the same circumstances, the products of tissue breakdown cannot be excreted, and the dangers of fulminating uremia and hyperkalemia may render any delay extremely hazardous. When in a patient with oliguria who has appeared to be doing relatively well there develops a sudden increase in the plasma concentration of NPN or potassium, occult infection or necrosis should be suspected. A careful examination of the patient may show an early subphrenic abscess, a pelvic abscess, or an area of infection hidden by a cast (as in HB).

The serum concentration of potassium and NPN is, at best, only a rough index of a loss of tissue viability. Meroney,[2] dealing with a similar series of patients, has suggested that the ratio of serum phosphate to nonprotein nitrogen is a better index of tissue necrosis than is the concentration of serum potassium or nonprotein nitrogen alone.

A striking feature in patients with acute renal failure was the delayed appearance of granulation tissue and wound healing. Frequently the onset of diuresis and a fall in the serum nonprotein nitrogen seemed to coincide with a sudden increase of granulation tissue and accelerated wound healing. This has been noted by others.[12] The expectation of delayed healing must be kept in mind when the wounds of these patients are being treated or operation is contemplated. Dehiscence occurs frequently. In sutured wounds the choice of suture material must be guided by the knowledge that effective wound healing will not begin until renal function returns and uremia abates. Delayed wound healing may result in a vicious cycle; deficient tissue repair and poor localization of infection contribute to further infection, with increased tissue injury and necrosis. This tissue injury, in turn, contributes to an increased degree of uremia; thus wound healing is further delayed, and the opportunity for further infection and necrosis is enhanced.

Excision of necrotic and infected tissues, is, of course, most readily applied in those patients in whom the involved areas are in the extremities. Here the entire area affected can be removed, leaving the smallest possible surface exposed to reinfection. Such patients should have the best prognosis, and it should be noted that both patients in our third group were of this type.

Summary and Conclusions

The case histories of eight patients with acute renal failure are presented.

Accumulation of potassium and nonprotein nitrogen in the serum of patients with renal insufficiency is accelerated in the presence of large amounts of necrotic tissue or infection. Fatal myocardial potassium intoxication may develop rapidly and is a recurrent hazard.

Control of the hyperkalemia and uremia in these patients is best accomplished through frequent use of the artificial kidney. Nevertheless, the patient's clinical condition may again deteriorate unless the necrotic tissue is removed or the infection brought under control. Amputation, debridement, and drainage, therefore, must be undertaken at the earliest evidence of abscess or necrosis, even in profoundly ill patients.

Delayed wound healing is to be expected in these patients. This should not affect the decision for definitive operation, but may be

a factor in the choice of incisions and the suture materials employed.

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Reconstruction of the Esophagus and Stomach with Segments of the Colon*

WILLIAM E. NEVILLE, M.D., and GEORGE H. A. CLOWES Jr., M.D., Cleveland

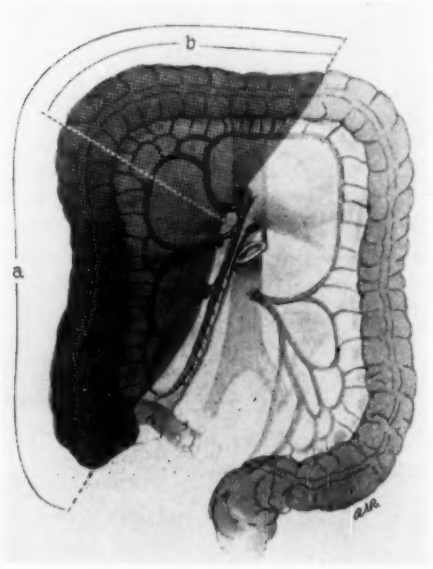

Fig. 1.—In esophageal reconstructions, the colon is mobilized as depicted in (*a*) from the cecum to the distal transverse. The right colic and a branch of the ileocolic arteries are transected close to their origin. The colon is divided proximally at the ileocolic valve and the opening in the cecum closed. Distally, the bowel is transected near the splenic flexure. The entire segment of bowel is suspended upon a vascular pedicle of the middle colic artery and vein.

For reconstructions of the lower end of the esophagus and stomach, a pie-shaped segment of transverse colon is mobilized, as depicted in (*b*).

* Surgery Illustrated. Shown as scientific exhibit of the Section on Surgery, General and Abdominal, at the 106th Annual Meeting of the American Medical Association, New York, June 3-7, 1957.

From the Department of Surgery, Western Reserve University School of Medicine at City Hospital.

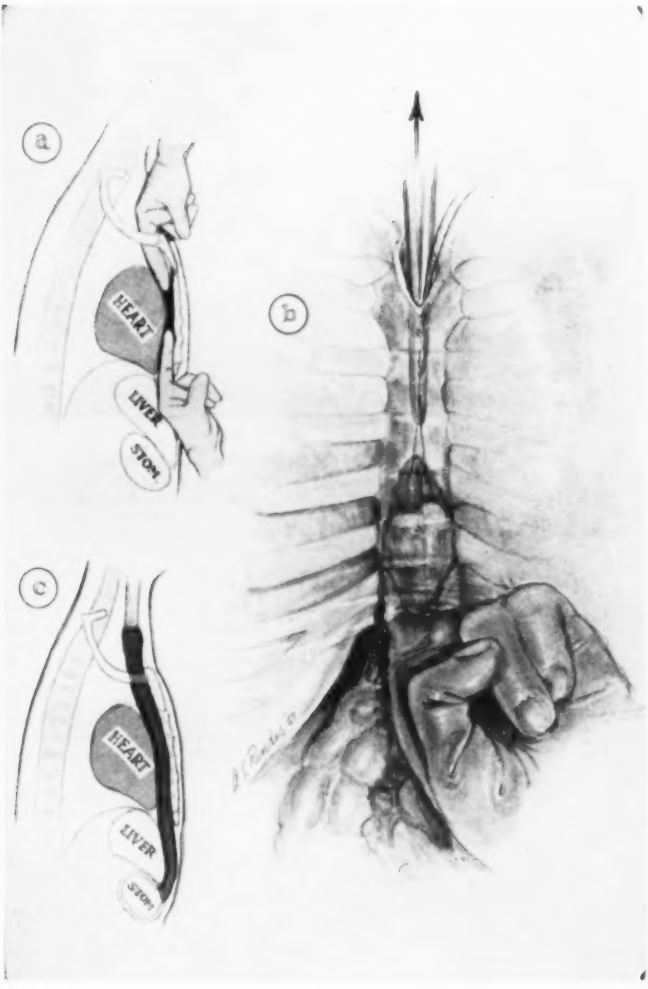

Fig. 2. — For cervical lesions the proximal end of the colon is displaced into the neck through an anterior mediastinal tunnel. The esophagus is exposed in the neck through an incision along the anterior border of the right sternocleidomastoid muscle. By blunt and sharp dissection (*a*) from the neck and abdomen, a tunnel is created in the anterior mediastinum. In (*b*) the cecum is gently pulled into the neck. The cross section (*c*) depicts the completed procedure, with the cecum anastomosed to the cervical esophagus and the distal transverse colon sutured to the stomach.

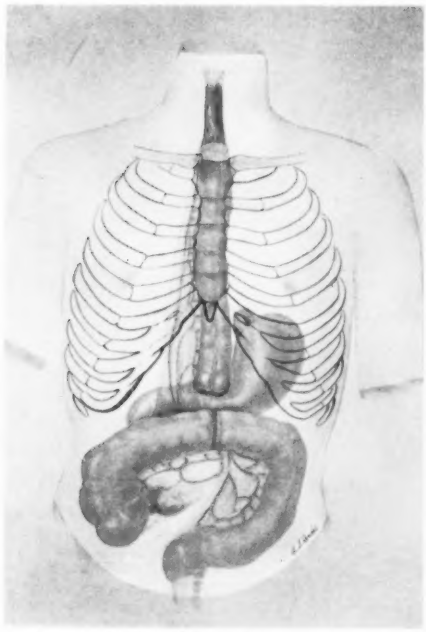

Figure 3

Fig. 3.—Completed esophageal reconstruction through an anterior mediastinal tunnel. In children, because of the redundancy of the transverse colon and the thin, pliable mesentery, sufficient length of bowel may occasionally be obtained without using the cecum for the high anastomosis.

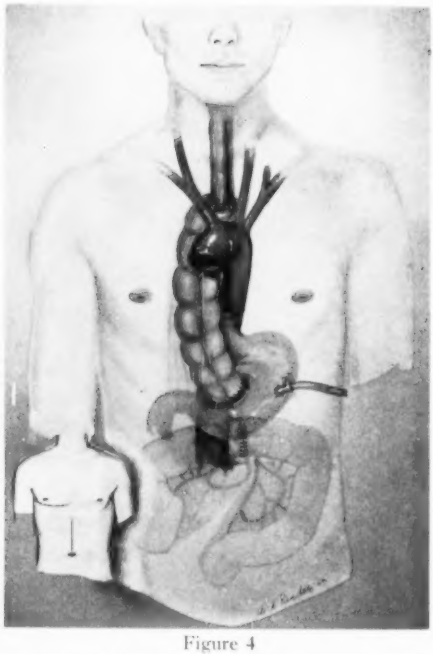

Figure 4

Fig. 4.—Intrathoracic lesions about the aortic arch are approached through a right thoracotomy and upper right paramedian or midline incision. The patient is positioned on the operating table at a 45-degree angle. This allows the thoracic team to perform an adequate resection of the esophagus and invert the lower end. Simultaneously, the colon can be mobilized by the abdominal surgeon. Here the colon is delivered into the chest through an opening in the diaphragm anterior to the right lobe of the liver. It is placed in front of the hilus of the lung. An end-to-end ileocolostomy establishes lower gastrointestinal continuity. A pyloroplasty is performed to provide adequate drainage to the vagotomized stomach. A gastrostomy is done to decompress the stomach in the early postoperative period and subsequently to feed the patient.

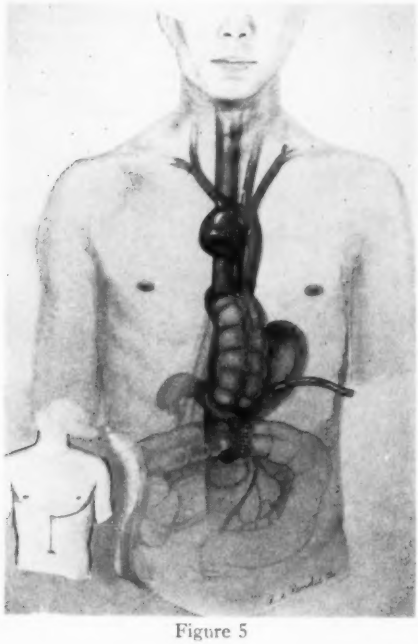

Figure 5

Fig. 5.—Intrathoracic esophageal lesions below the aortic arch are approached through separate left abdominal and thoracic incisions. It has not been necessary to cut across the costal margins. The diaphragm can be transected from the hiatus outward. In this situation it may not be necessary to mobilize the entire right colon. The transverse colon is usually of sufficient length to substitute for the resected esophagus. The bowel is replaced in the bed of the resected esophagus and the entire area repleuralized. If the stomach is normal, the opening in the cardia is closed and the distal end of the colon anastomosed to the stomach anteriorly. However, if a resection of a portion of the stomach is necessary, the distal end of the colon segment may be anastomosed end-to-end to the remaining portion of the stomach. A pyloroplasty and a tube gastrostomy are performed. A colocolostomy completes the operative procedure.

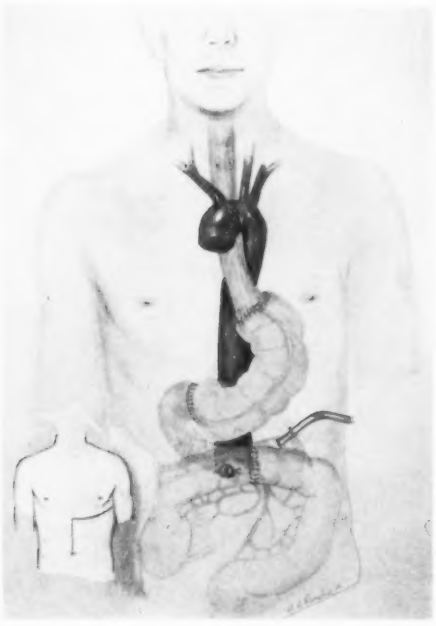

Fig. 6.—A left thoracoabdominal incision is used for the total gastrectomy. Following resection of the stomach a segment of transverse colon suspended upon a vascular pedicle is interpolated isoperistaltically between the esophagus and the duodenum. A feeding jejunostomy is performed upon completion of the colocolostomy.

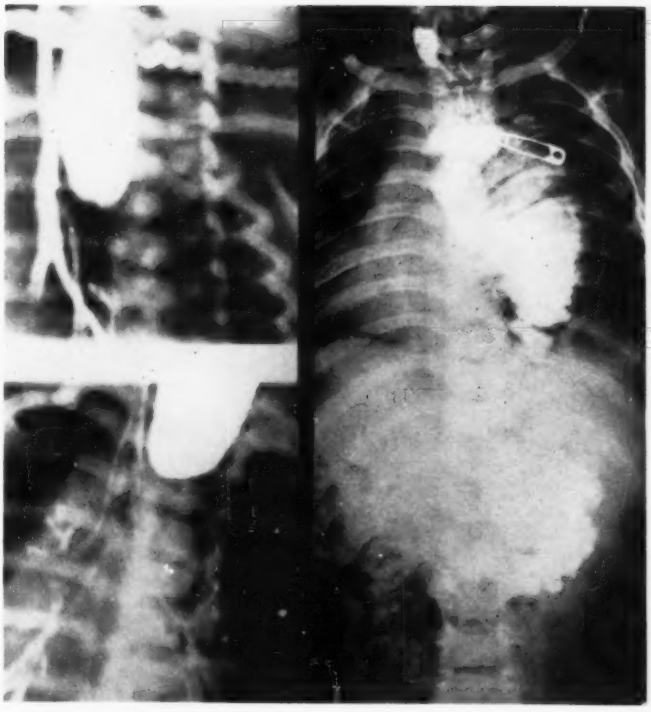

Fig. 7.—The x-ray on the left depicts a tracheoesophageal fistula with atresia. Division of the fistula, resection of the atretic esophagus with inversion of the lower end, exteriorization of the blind upper end, and a tube-feeding gastrostomy were performed at the age of 4 days. Esophagogastric continuity was established with an anterior mediastinal colon transplant at the age of one year. The x-ray on the right shows normal passage of barium through the reconstructed esophagus. This child is now 3 years old and is in excellent condition.

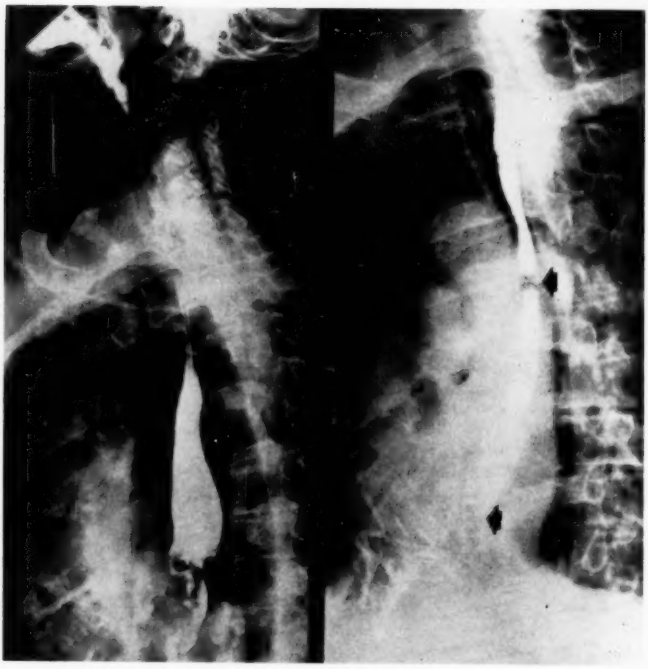

Fig. 8.—These are pre- and postoperative x-rays of a 65-year-old man who had a resection of an advanced carcinoma behind the aortic arch in 1954. The arrows in the film on the right point to the proximal and distal suture lines of the colon transplant.

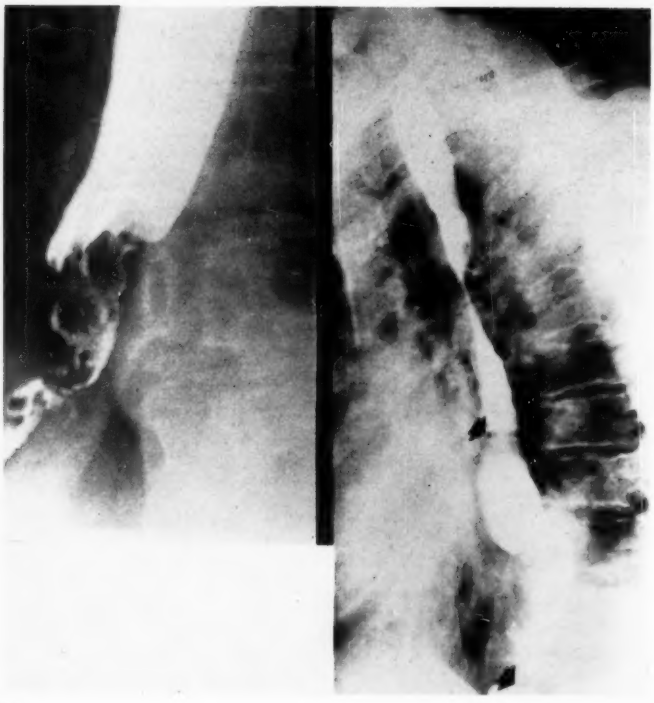

Fig. 9.—These x-rays demonstrate a large carcinoma of the lower end of the esophagus, which was adequately resected, with the restoration of a normal swallowing mechanism with a segment of colon. The proximal arrow shows the esophagocolostomy, and the distal arrow, the cologastrostomy. This 55-year-old man ate normally and was in good health for two years.

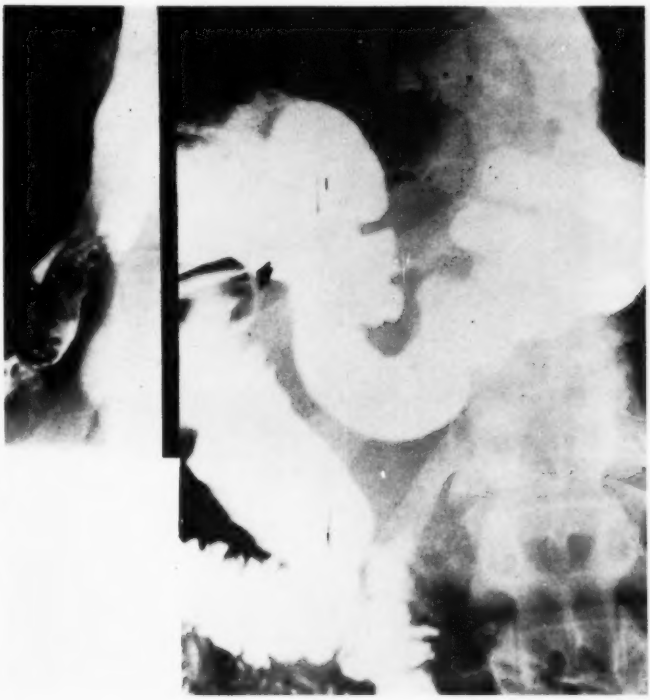

Fig. 10.—These prints show the pre- and post-operative x-rays of the 54-year-old man who underwent a resection of the distal esophagus and the major portion of his stomach for an advanced squamous-cell carcinoma with extensive gastric involvement. An adequate segment of colon was interposed in an isoperistaltic manner between the esophagus and the antrum of the stomach. This man gained 45 lb. and went back to steel construction work.

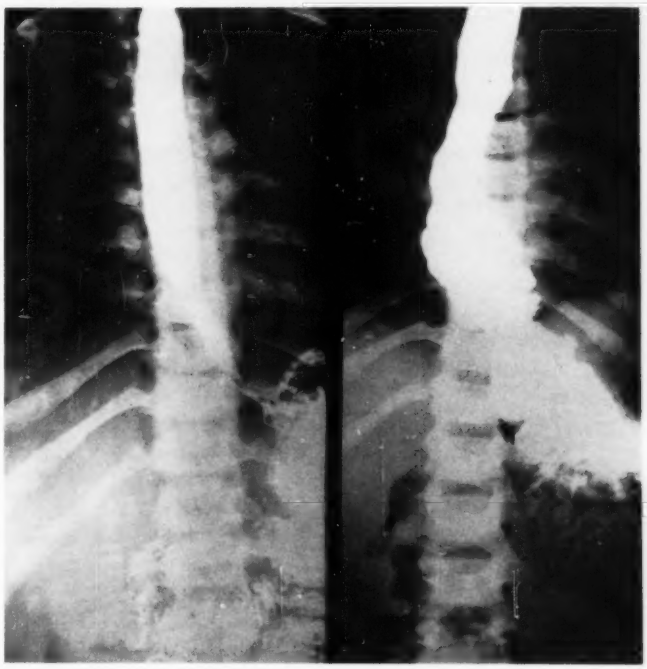

Fig. 11.—The x-rays on the left show a stricture of the lower end of the esophagus in an 8-year-old boy following ingestion of hydrochloric acid. Despite repeated esophageal dilatations, dysphagia and vomiting persisted. One year prior to this report, the lower end of his esophagus was resected and a segment of transverse colon interpolated between the remaining esophagus and the stomach, as seen in the x-ray on the right. The arrows point to the proximal and distal suture lines. At the moment this child is eating normally and is a strong, healthy child.

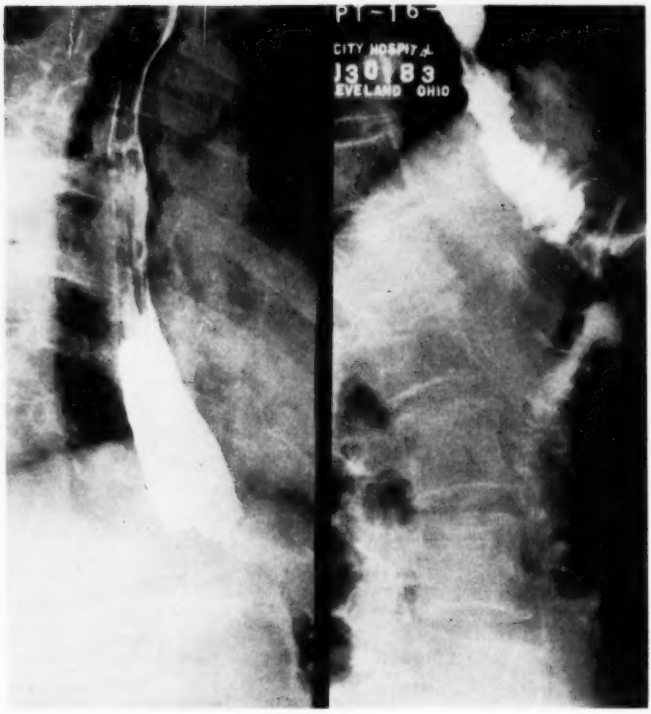

Fig. 12.—The x-ray on the left shows a carcinoma arising in the lower end of the esophagus with extensive involvement of the stomach in a 68-year-old man. A resection of the distal esophagus and a total gastrectomy were performed. A segment of transverse colon was used to establish esophagoduodenal continuity. The patient lived comfortably for one year before succumbing to his carcinoma.

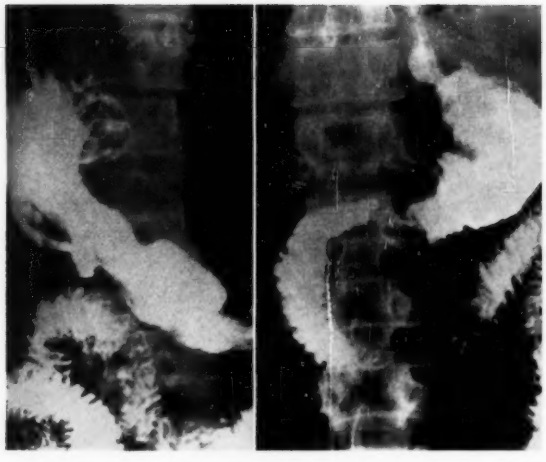

Fig. 13.—A 50-year-old man had an infiltrating carcinoma along the greater curvature, as seen in the roentgenogram on the right. A total gastrectomy was performed two years prior to this report and a segment of transverse colon interposed in an antiperistaltic manner between the esophagus and the duodenum, as seen in the x-ray on the left. He can eat in a normal manner, with no evidence of regurgitation. Fluoroscopically, he does have some regurgitation of barium into the esophagus, due to the reverse peristalsis in the colon segment.

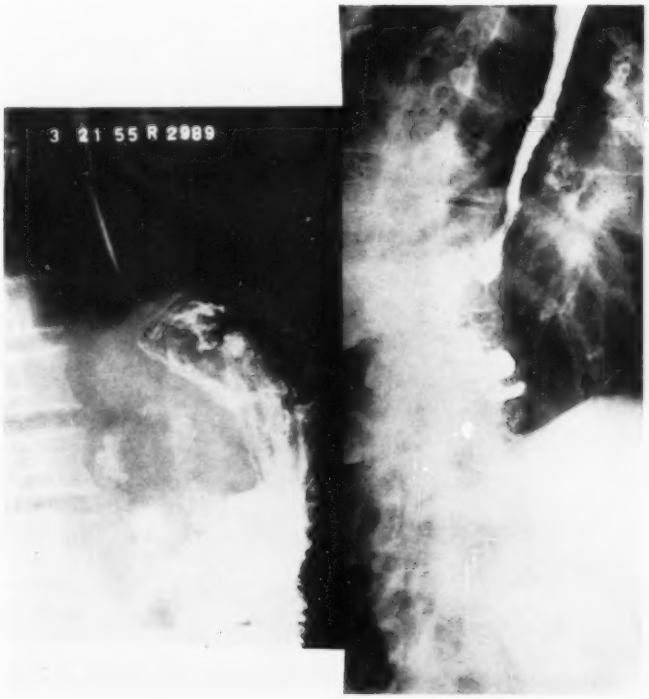

Fig. 14.—These are the pre- and postoperative x-rays of a 56-year-old man who had a resection of his lower esophagus and all of his stomach except the antrum for a large polypoid carcinoma of the fundus. A segment of colon was interpolated between the esophagus and the remaining portion of his stomach. Thirty-six months have elapsed since his surgery. He can eat in a normal manner and works every day in a steel mill.

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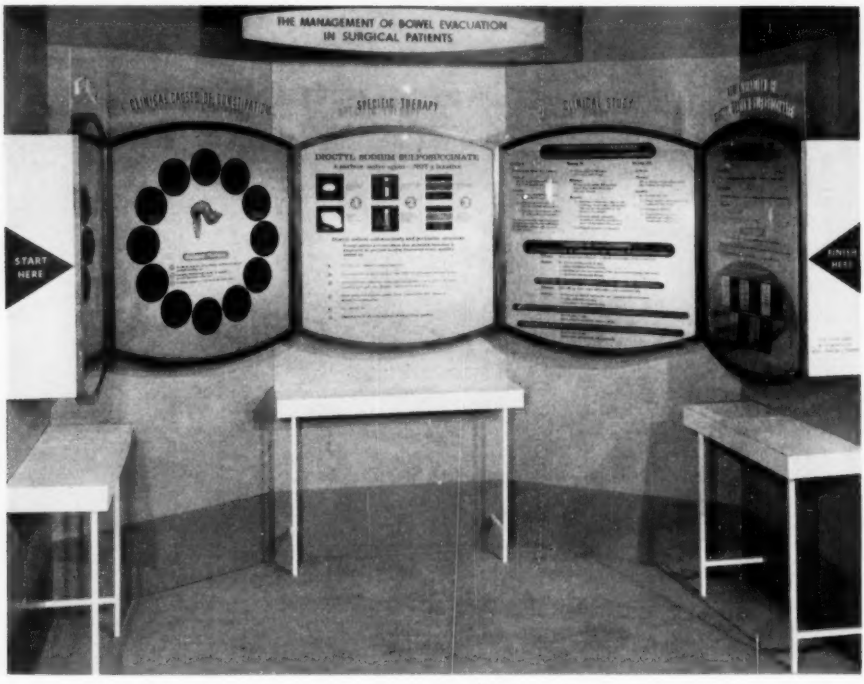
The Management of Bowel Evacuation in Surgical Patients*

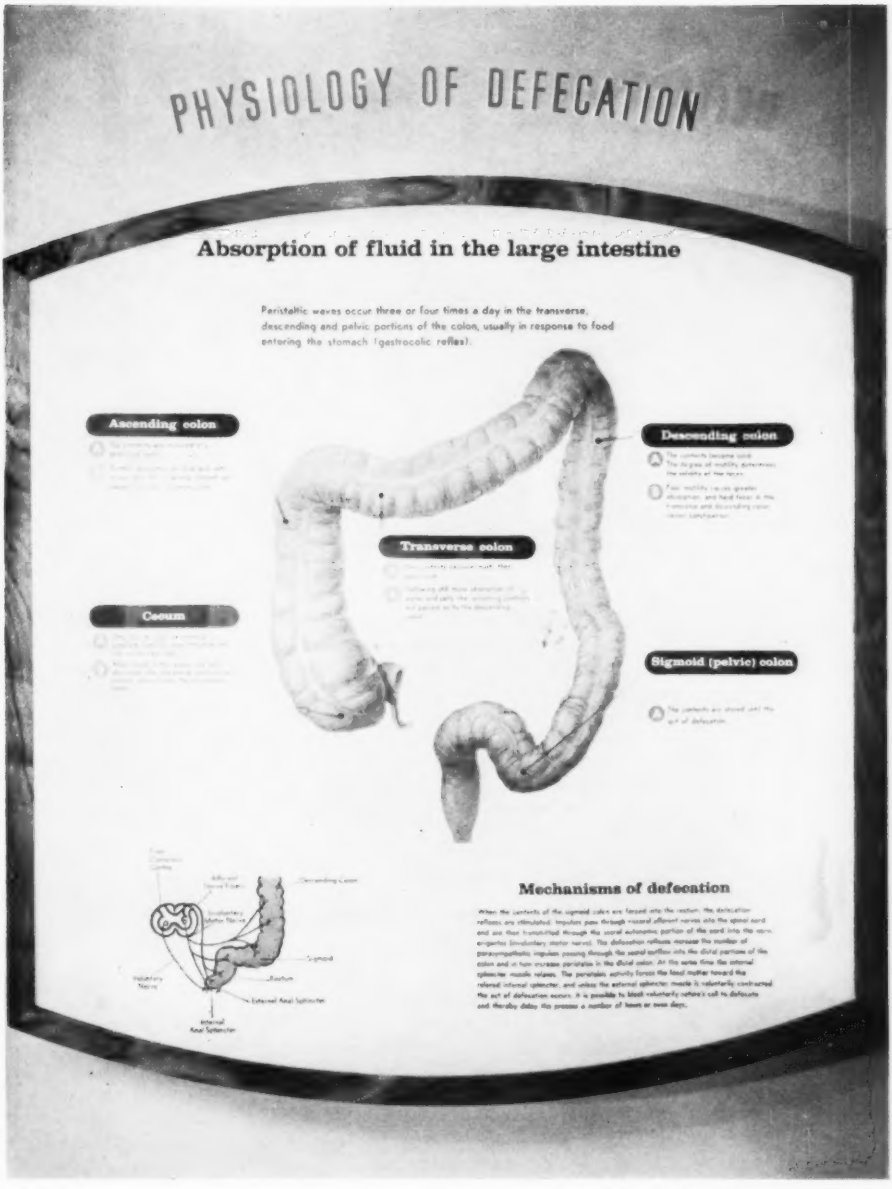
ROBERT TURELL, M.D., New York



Introduction

Many patients who undergo anorectal operations require an agent that will promote the smooth passage of stool of normal or near-normal bulk at the first postoperative bowel action. Dioctyl sodium sulfosuccinate U. S. P. (Colace) has proved to be a safe agent for this purpose, after surgical procedures for pilonidal disease, and in colostomized patients after abdominoperineal resection of the rectum. This compound is also receiving a trial after resection and anastomosis of the colon and following electrocoagulation of adenomas. In my practice, following the performance of anorectal operations, use of dioctyl sodium sulfosuccinate is now standard procedure in place of conventional liquid petrolatum, which has been almost completely superseded. A stimulant-laxative (pericolace) is required in addition to dioctyl sodium sulfosuccinate for some patients, mostly elderly persons, as well as for the preponderance of those patients who are habituated to cathartics. Occasionally a flushing saline enema with or without dioctyl sodium sulfosuccinate solution is given for the expulsion of postoperative fecal accumulation in the ampulla.

* Surgery Illustrated. Shown as scientific exhibit of the Section on Surgery, General and Abdominal, at the 106th Annual Meeting of the American Medical Association, New York, June 3-7, 1957.


PHYSIOLOGY OF DEFECATION
Absorption of fluid in the large intestine
Peristaltic waves occur three or four times a day in the transverse, descending and pelvic portions of the colon, usually in response to food entering the stomach (gastrocolic reflex).
Ascending colon
Descending colon
Transverse colon
Cecum
Sigmoid (pelvic) colon
Mechanisms of defecation

PANEL I

Physiology of Defecation

Absorption of Fluid in the Large Intestine

Peristaltic waves occur three or four times a day in the transverse, descending, and pelvic portions of the colon, usually in response to food entering the stomach (gastrocolic reflex).

I. Cecum

A. One liter or more of material is emptied from the small intestine into the cecum each day.

B. After much of the water and salts is absorbed, the remaining contents are passed upward into the ascending colon.

II. Ascending Colon

A. The contents are received in a semifluid form.

B. Further absorption of fluid and salts occurs, and the remaining contents are passed into the transverse colon.

III. Transverse colon

A. The contents become mush, then semimush.

B. After still more absorption of water and salts, the remaining contents are passed on the descending colon.

IV. Descending colon

A. The contents become solid. The degree of motility determines the solidity of the feces.

B. Poor motility causes greater absorption, and hard feces in the transverse and descending colon causes constipation.

V. Sigmoid (pelvic) colon

A. The contents are stored until the act of defecation.

MECHANISMS OF DEFECATION

When the contents of the sigmoid colon are forced into the rectum, the defecation reflexes are stimulated. Impulses pass through visceral afferent nerves into the spinal cord and are then transmitted through the sacral autonomic portion of the cord into the nervi erigentes (involuntary motor nerves). The defecation reflexes increase the number of parasympathetic impulses passing through the sacral outflow into the distal portions of the colon and, in turn, increase peristalsis in the distal colon. At the same time the internal sphincter muscle relaxes. The peristalsis activity forces the fecal matter toward the relaxed internal sphincter, and unless the external sphincter muscle is voluntarily contracted, the act of defecation occurs. It is possible to block voluntarily nature's call to defecate and thereby delay the process a number of hours or even days.

PANEL II

Clinical Causes of Constipation

Visual No. 3 (Frustrated man [face]).—Psychosomatically determined constipation.

Visual No. 4 (Man working in hot sun).—Loss of body fluid via the integument.

Visual No. 5 (Person eating).—Low-residue diets; constipating diets.

Visual No. 6 (Man reaching into medicine cabinet for laxative).—Cathartic habit.

Visual No. 7 (Man in a wheel chair).—Constipation caused by general debility.

Visual No. 8 (Man rushing out of house).—Faulty bowel habits.

Visual No. 9 (Very frail man).—Deficiency states.

Visual No. 10 (Face covered with rash).—Allergic sensitivity.

Visual No. 11 (Man reading prescription).—Medications which depress bowel motility.

Visual No. 12 (Small girl wearing leg braces).—Diseases affecting the innervation of the bowel.

Visual No. 13 (Obviously pregnant woman).—Obstruction due to extrinsic conditions.

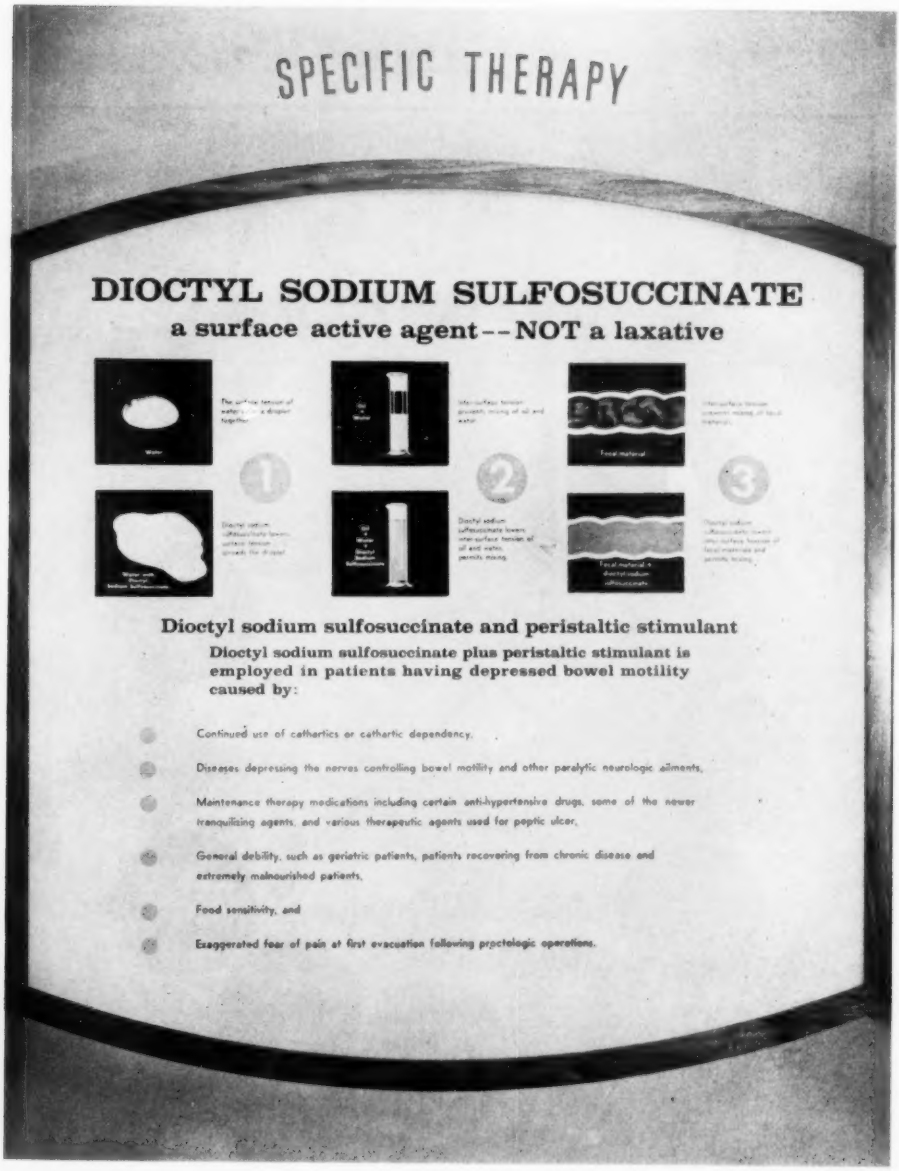
Visual No. 14 (Man suffering from anal ulcer [sitting position]).—Intrinsic bowel disease.

General Therapy

1. Provide an adequate and nutritionally well-balanced diet with adequate roughage, but
2. Emphasize breakfast large enough to promote a powerful gastrocolic reflex, and
3. Emphasize regularity of response to the call to stool.

CLINICAL CAUSES OF CONSTIPATION
PSYCHOSOMATICALLY DETERMINED CONSTIPATION
INTRINSIC BOWEL DISEASE
OBSTRUCTION DUE TO EXTRINSIC CONDITIONS
DISEASES AFFECTING THE INNERVATION OF THE BOWEL
MEDICATIONS WHICH UPSET BOWEL
ALLERGIC
IRRITABLE COLON
FAULTY BOWEL HABITS
CONSTIPATION CAUSED BY GENERAL DEBILITY
CATHARTIC HABIT
LOW-RESIDUE DIETS CONSTIPATING DIETS
LOSS OF BODY FLUID VIA THE INTEGUMENT
General Therapy
1 Provide an adequate and nutritionally well-balanced diet with adequate roughage, but
2 Emphasize breakfast large enough to promote a powerful gastrocolic reflex, and
3 Emphasize regularity of response to the call to stool.

(Panel II)


SPECIFIC THERAPY
DIOCTYL SODIUM SULFOSUCCINATE
a surface active agent--NOT a laxative
Water
Water
Fecal material
1
2
3
Water with Dioctyl Sodium Sulfosuccinate
Oil + Water + Dioctyl Sodium Sulfosuccinate
Fecal material + dioctyl sodium sulfosuccinate
Dioctyl sodium sulfosuccinate and peristaltic stimulant
Dioctyl sodium sulfosuccinate plus peristaltic stimulant is employed in patients having depressed bowel motility caused by:
Continued use of cathartics or cathartic dependency.
Diseases depressing the nerves controlling bowel motility and other paralytic neurologic ailments.
Maintenance therapy medications including certain anti-hypertensive drugs, some of the newer tranquilizing agents, and various therapeutic agents used for peptic ulcer.
General debility, such as geriatric patients, patients recovering from chronic disease and extremely malnourished patients.
Food sensitivity, and
Exaggerated fear of pain at first evacuation following proctologic operations.

PANEL III

Specific Therapy

Dioctyl Sodium Sulfosuccinate

A Surface-Active Agent—NOT a Laxative

I. Water: The surface tension of water holds a droplet together.
Water with dioctyl sodium sulfosuccinate: Dioctyl sodium sulfosuccinate lowers

surface tension . . . spreads the droplet.

II. Oil+water: Intersurface tension prevents mixing of oil and water.
Oil+water+dioctyl sodium sulfosuccinate: Dioctyl sodium sulfosuccinate lowers intersurface tension of oil and water, permits mixing.

III. Fecal material: Intersurface tension prevents mixing of fecal materials.
Fecal material+dioctyl sodium sulfosuccinate: Dioctyl sodium sulfosuccinate lowers intersurface tension of fecal materials and permits mixing.

Dioctyl Sodium Sulfosuccinate and Peristaltic Stimulant

Dioctyl sodium sulfosuccinate plus peristaltic stimulant is employed in patients having depressed bowel motility caused by

Continued use of cathartics or cathartic dependency.

Diseases depressing the nerves controlling bowel motility and other paralytic neurologic ailments.

Maintenance therapy medications, including certain antihypertensive drugs, some of the newer tranquilizing agents, and various therapeutic agents used for peptic ulcer.

General debility, such as geriatric patients, patients recovering from chronic disease, and extremely malnourished patients.

Food sensitivity, and

Exaggerated fear of pain at first evacuation following proctologic operations.

PANEL IV

Clinical Study

Series of 105 Patients Operated on for Anorectal Conditions

Group I

20 patients not habituated to cathartics.

Therapy: 200 mg. of dioctyl sodium sulfosuccinate daily in two divided doses.

Results: 16—Formed softer but homogeneous feces within 72 hours.
3—Required peristaltic stimulant and dioctyl sodium sulfosuccinate.
1—Required a saline enema in addition to dioctyl sodium sulfosuccinate.

The four patients who required peristaltic stimulant or a saline enema in addition to dioctyl sodium sulfosuccinate were over 51 years of age.

Group II

22 patients cathartic habituated and over 51 years of age.

Therapy: 300 mg. of dioctyl sodium sulfosuccinate daily in three divided doses, plus a peristaltic stimulant.

Results: 3—Remained on maintenance dose of 100 to 200 mg. of dioctyl sodium sulfosuccinate following the administration of only one dose of a cathartic.
1—Required periodic stimulation by means of cathartics in addition to use of dioctyl sodium sulfosuccinate.
18—Required stimulation of the bowel.

Group III

63 patients (under 51 years of age)

Therapy: 300 mg. of dioctyl sodium sulfosuccinate daily in three divided doses.

Results: 55—Formed soft feces.
3—Feces failed to soften because of inadequate fluid intake.
2—Developed diarrhea.
3—Feces softened but required flushing saline enema in addition to use of dioctyl sodium sulfosuccinate.

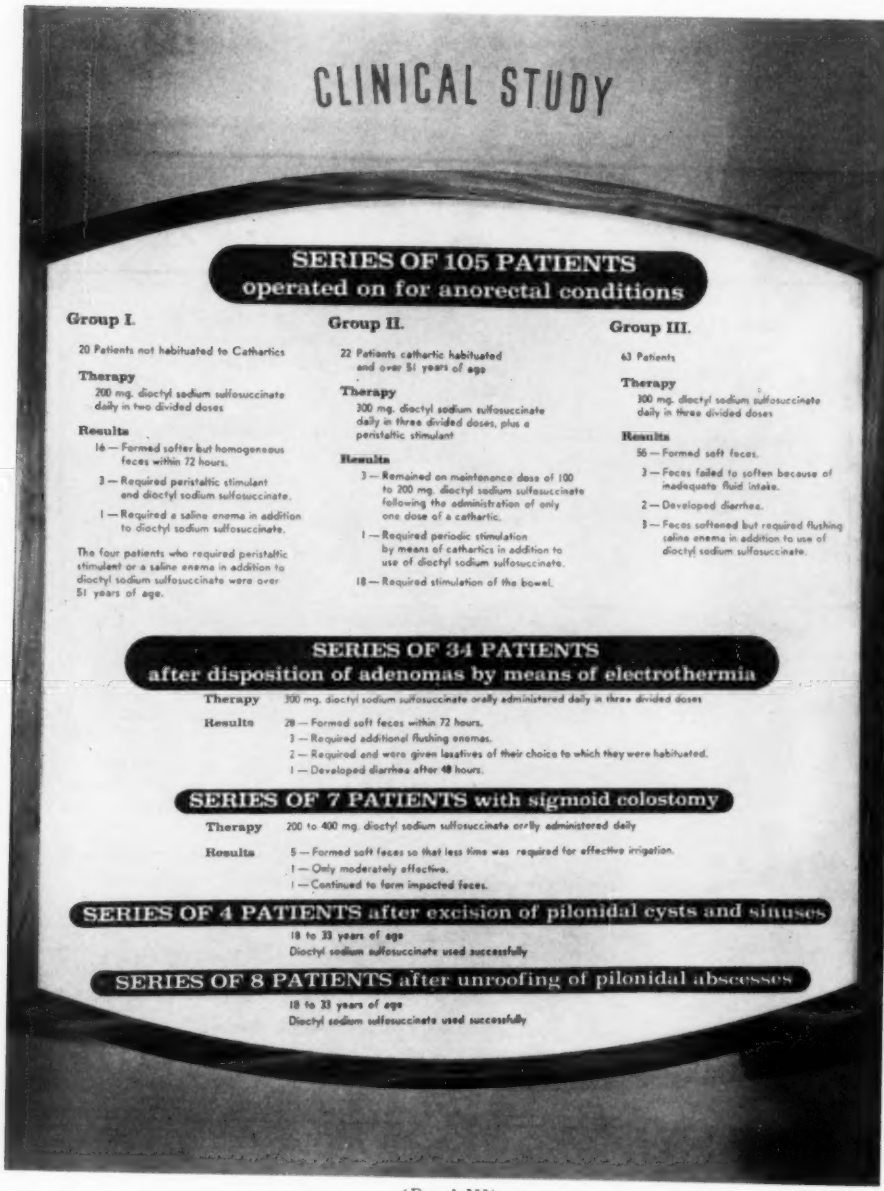
Series of 34 Patients After Disposition of Adenomas by Means of Electrothermia

Therapy: 300 mg. of dioctyl sodium sulfosuccinate orally, administered daily in three divided doses.

Results: 28—Formed soft feces within 72 hours.
3—Required additional flushing enemas.
2—Required and were given laxatives of their choice to which they were habituated.
1—Developed diarrhea after 48 hours.

Series of 14 Patients with Sigmoid Colostomy

Therapy: 200 to 400 mg. of dioctyl sodium sulfosuccinate orally administered daily.


CLINICAL STUDY
SERIES OF 105 PATIENTS
operated on for anorectal conditions
Group I.
20 Patients not habituated to Cathartics
Therapy
200 mg. dioctyl sodium sulfosuccinate daily in two divided doses
Results
16 — Formed softer but homogeneous feces within 72 hours.
3 — Required peristaltic stimulant and dioctyl sodium sulfosuccinate.
1 — Required a saline enema in addition to dioctyl sodium sulfosuccinate.
The four patients who required peristaltic stimulant or a saline enema in addition to dioctyl sodium sulfosuccinate were over 51 years of age.
Group II.
22 Patients cathartic habituated and over 51 years of age
Therapy
300 mg. dioctyl sodium sulfosuccinate daily in three divided doses, plus a peristaltic stimulant
Results
3 — Remained on maintenance dose of 100 to 200 mg. dioctyl sodium sulfosuccinate following the administration of only one dose of a cathartic.
1 — Required periodic stimulation by means of cathartics in addition to use of dioctyl sodium sulfosuccinate.
18 — Required stimulation of the bowel.
Group III.
63 Patients
Therapy
300 mg. dioctyl sodium sulfosuccinate daily in three divided doses
Results
56 — Formed soft feces.
3 — Feces failed to soften because of inadequate fluid intake.
2 — Developed diarrhea.
3 — Feces softened but required flushing saline enema in addition to use of dioctyl sodium sulfosuccinate.
SERIES OF 34 PATIENTS
after disposition of adenomas by means of electrothermia
Therapy 300 mg. dioctyl sodium sulfosuccinate orally administered daily in three divided doses
Results 28 — Formed soft feces within 72 hours.
3 — Required additional flushing enemas.
2 — Required and were given laxatives of their choice to which they were habituated.
1 — Developed diarrhea after 48 hours.
SERIES OF 7 PATIENTS with sigmoid colostomy
Therapy 200 to 400 mg. dioctyl sodium sulfosuccinate orally administered daily
Results 5 — Formed soft feces so that less time was required for effective irrigation.
1 — Only moderately effective.
1 — Continued to form impacted feces.
SERIES OF 4 PATIENTS after excision of pilonidal cysts and sinuses
18 to 33 years of age
Dioctyl sodium sulfosuccinate used successfully
SERIES OF 8 PATIENTS after unroofing of pilonidal abscesses
18 to 33 years of age
Dioctyl sodium sulfosuccinate used successfully

(Panel IV)

Results: 9—Formed soft feces so that less time was required for effective irrigation.
3—Only moderately effective.
1—Continued to form impacted feces.
1—No change.

Series of 4 Patients After Excision of Pilonidal Cysts and Sinuses
18 to 33 years of age

Dioctyl sodium sulfosuccinate used successfully

Series of 8 Patients After Unroofing of Pilonidal Abscesses

18 to 33 years of age

Dioctyl sodium sulfosuccinate used successfully

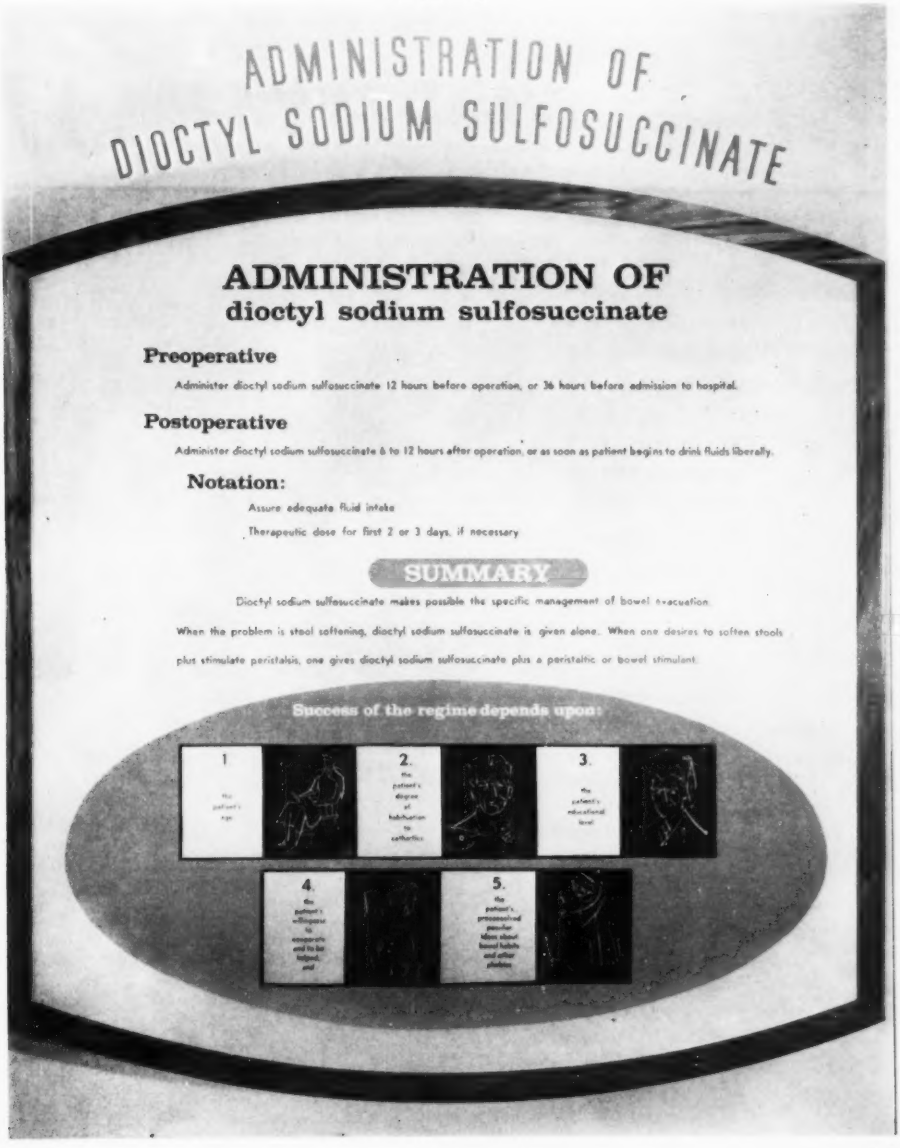
PANEL V

Administration of Dioctyl Sodium Sulfosuccinate

Preoperative

Administer dioctyl sodium sulfosuccinate 12 hours before operation, or 36 hours before admission to hospital.

(Panel V)


ADMINISTRATION OF
DIOCTYL SODIUM SULFOSUCCINATE
ADMINISTRATION OF
dioctyl sodium sulfosuccinate
Preoperative
Administer dioctyl sodium sulfosuccinate 12 hours before operation, or 36 hours before admission to hospital.
Postoperative
Administer dioctyl sodium sulfosuccinate 6 to 12 hours after operation, or as soon as patient begins to drink fluids liberally.
Notation:
Assure adequate fluid intake
Therapeutic dose for first 2 or 3 days, if necessary
SUMMARY
Dioctyl sodium sulfosuccinate makes possible the specific management of bowel evacuation.
When the problem is stool softening, dioctyl sodium sulfosuccinate is given alone. When one desires to soften stools plus stimulate peristalsis, one gives dioctyl sodium sulfosuccinate plus a peristaltic or bowel stimulant.
Success of the regime depends upon:
1
2.
3.
4.
5.

Postoperative

Administer dioctyl sodium sulfosuccinate 6 to 12 hours after operation, or as soon as patient begins to drink fluids liberally.

Notation:

1. Assure adequate fluid intake.
2. Therapeutic dose for first two or three days, if necessary.

Summary

Dioctyl sodium sulfosuccinate makes possible the specific management of bowel evacuation. When the problem is stool softening, dioctyl sodium sulfosuccinate is given alone. When one desires to soften stools and stimulate peristalsis, one gives dioctyl sodium sulfosuccinate plus a peristaltic or bowel stimulant (Pericolace)

Success of the Regimen Depends upon:

1. The patient's age (Visual No. 15: elderly lady in rocking chair)
2. The patient's degree of habituation to cathartics (Visual No. 16: person taking a laxative)
3. The patient's educational level (Visual No. 17: scholarly-looking graduate)
4. The patient's willingness to cooperate and to be helped (Visual No. 18: person reading from list of instructions)
5. The patient's preconceived peculiar ideas about bowel habits and other phobias (Visual No. 19: witch stirring a brew [superstition])

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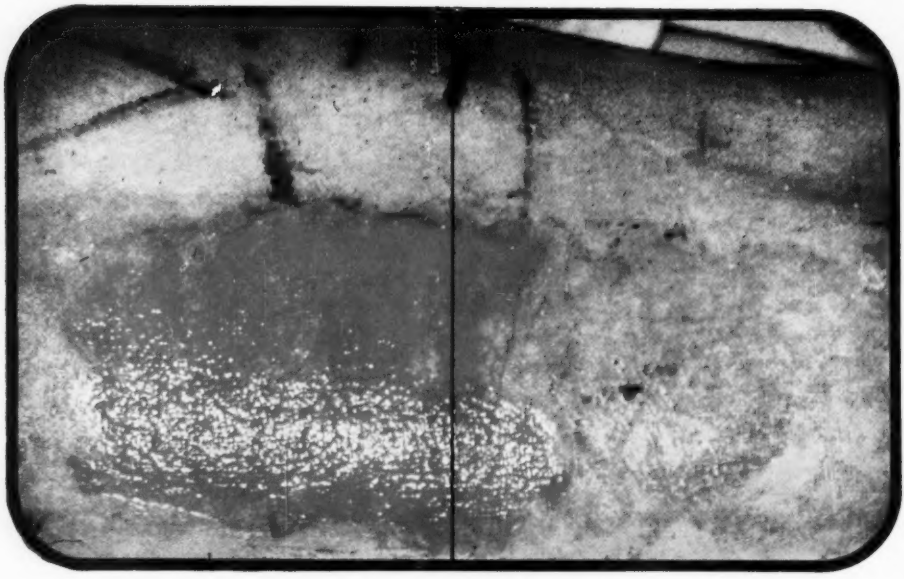

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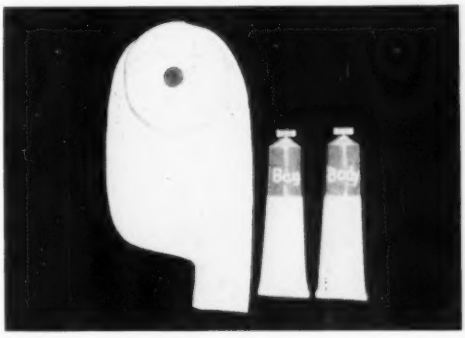

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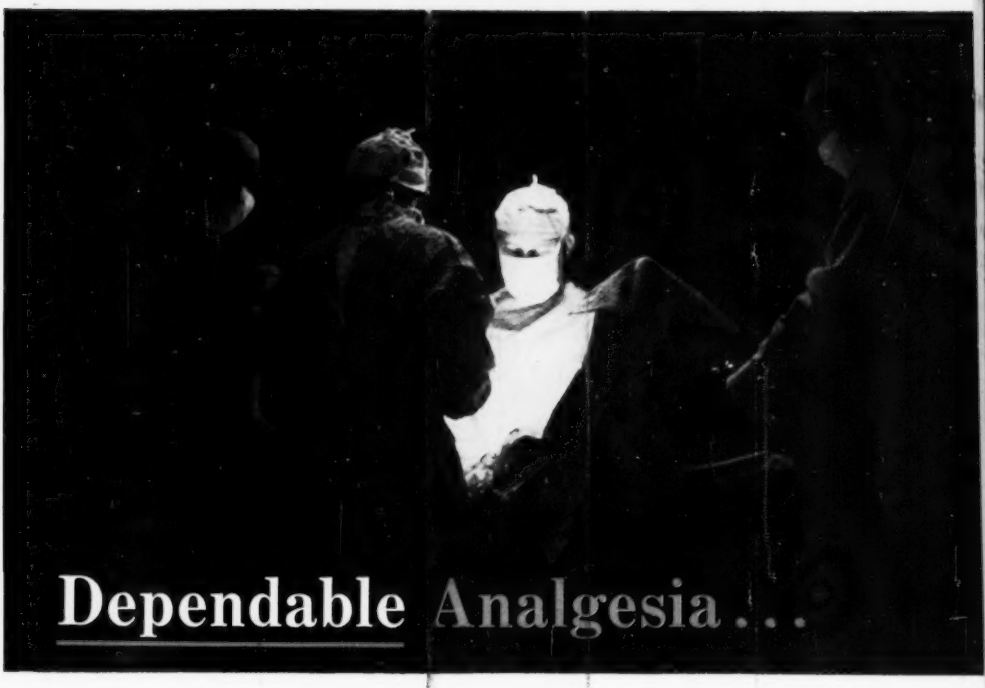

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